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# THE EFFECT OF HEMOGLOBIN AND RELATED PIGMENTS ON RENAL FUNCTIONS OF THE NORMAL AND ACIDOTIC DOG[1]

R. J. BING[2]

The effect of hemoglobin and related pigments on renal function has recently attracted interest owing to the frequency with which anuria was observed after the excretion of myoglobin following crush injuries (1) and during methemoglobinuria accompanying blackwater fever (2). Acidosis appears to be an important factor in production of renal lesions seen in these conditions (3). The present study deals with an investigation of the effect of acidosis alone, and combined with action of hemoglobin, methemoglobin, and myoglobin, on renal function, and a comparison of the information obtained through clearance studies with the pathological-histological lesions found in the kidney of animals injected with these substances.

## METHODS

The work of Smith and his coworkers (4) has made it possible to obtain quantitative data on renal function through the application of clearance tests. They have shown that the clearances of diodrast and p-aminohippuric acid at low plasma levels are identical (5). By virtue of their high extraction ratio the clearances of these substances closely approximate the effective renal plasma flow (4). P-aminohippuric acid was used rather than diodrast since its determination is rapid and offers fewer analytical hazards (5). Creatinine clearances were employed to measure glomerular filtration rate (6) as in the dog this substance is excreted by glomerular filtration alone and stimultaneous inulin and creatinine clearances are identical in this animal (7). As an additional renal function test, the study of the maximal tubular readsorptive capacity for glucose (Glucose Tm) was employed. This test is based on the observation of Shannon and

[1] Supported by a grant from the Josiah Macy, Jr., Foundation.

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coworkers (8) that in the dog the progressive elevation of the plasma glucose level leads to a point where the tubular readsorption of glucose reaches a constant, maximal rate. This maximal rate is a reproducible figure in any one animal (8). Since glucose is readsorbed by tubular mechanism, it is evident that pathological processes leading to tubular destruction might conceivably result in a decrease in the tubular transfer of glucose and a consequent fall in the glucose Tm. On the other hand, complete arrest of the filtration in a number of glomeruli will also produce a proportional decrease in Glucose Tm, since the tubules attached to the non-functioning glomeruli would fail to receive glucose (4). Consequently a fall in Glucose Tm might be either the result of complete cessation of glomerular filtration in a number of nephrons or the sequence of interference with the tubular transfer of this substance.

All experiments were performed on normal unanesthetized dogs. To assure high urine flows, ten grams of mannitol were added as a diuretic in all but four experiments. The substances used for determinations of the clearances were dissolved in from 100 to 200 cc. saline and infused into a leg or ear vein at a rate of 1.5 cc./min. In all but two animals in which methemoglobin was infused on three successive days, the pigment and clearance infusions were given simultaneously into a leg and an ear vein respectively by means of two mercury pumps. In the experiments dealing with the combined effects of blood pigment and acidosis, from 80 to 100 grams of ammonium chloride were given in distilled water through a stomach tube over a period of two days before infusion of the blood pigments was begun. In five animals the effect of intravenous infusion of lactic acid varying in strength from 5 to 10 per cent was studied; the action of hydrochloric acid (0.01–0.5 N) was investigated in four experiments. The blood urea, $CO_2$ combining power, blood and urine pH, and oxygen content were observed in a number of experiments for a period varying from two to eight days, provided the conditions of the animal permitted a follow-up. A series of animals receiving methemoglobin, myoglobin and hemoglobin were sacrificed at the end of the period of observation and the kidneys, liver and spleen were histologically examined.

Hemoglobin and methemoglobin were prepared from freshly citrated dog blood by repeated washings of the red cells with isotonic

saline. After siphoning off the washings, the concentrated red cell suspension was shaken up with one-fifth its volume of toluene for five minutes. The mixture was placed in the ice-box over night, and was centrifuged the next day at 2,000 revolutions per minute for 20 minutes. The toluene layer was then decanted, leaving a solid mass of crystalline hemoglobin in the tube. The crystals were washed twice with small amounts of ice-cold distilled water and dissolved in isotonic saline. After adjusting the pH to 7.4 with sodium bicarbonate, the solution was filtered twice and the hemoglobin concentration was estimated spectrometrically with a Coleman spectrophotometer. Methemoglobin was prepared by adding a 10 per cent excess of potassium ferricyanide to the washed cells immediately before shaking them with toluene. Myoglobin was obtained from dog muscle according to the method of Morgan (9). Its concentration was estimated spectrometrically as the alkaline hematin.

## EXPERIMENTAL

### *Action of hemoglobin and myoglobin*

The effect of from 4.1 to 10 grams of hemoglobin infused into the non-acidotic animal was investigated in three experiments. As seen in Table I the infusion of hemoglobin produced a slight fall in the glomerular filtration rate and the effective renal plasma flow. The infusion of hemoglobin into five animals made acidotic with ammonium chloride to a blood pH ranging from 6.90 to 7.29 (Table II) likewise resulted in a decline of the filtration rate during the infusion, the effective renal plasma flow falling to a proportionately greater extent during the first twenty minutes. Consequently, the filtration fraction rose slightly indicating efferent arteriolar constriction. The urinary pigment excreted by these animals was identified as hemoglobin by means of spectroscopic examination. After two or three days the clearance values returned to their control figures, demonstrating that *the infusion of crystalline hemoglobin into both the normal and the acidotic animal failed to produce any irreversible impairment of renal function.* This conclusion was further substantiated by histological examinations which failed to reveal renal lesions.

The work of Bywaters (1, 10) has indicated that the excretion of myoglobin in the presence of acidosis plays a major role in the pro-

duction of anuria following crushing injuries. Therefore, the effect of the infusion of this pigment on renal function was studied in five animals made acidotic with ammonium chloride. From 4.7 to 7.3 grams of the pigment were dissolved in 450 cc. of saline, and subsequently infused into the leg vein (Table II). The pH at the beginning of the infusion varied from 7.10 to 7.20. The infusion of the pigment was followed by an increase in urine flow and a slight fall in the glo-

TABLE I

*Effect of hemoglobin and methemoglobin injections on renal function of normal dogs*

| EXP. | NO. DOG | DATE | GM. PIGMENT INJECTED | RATE OF INFUSION | pH OF BLOOD DAY | FILTRATION RATE | | | EFFECTIVE RENAL PLASMA FLOW | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Before infusion | At end of infusion | Follow up | Before infusion | At end of infusion | Follow up |
| **Hemoglobin injections** | | | | | | | | | | | |
| 16D | 1 | 7–31–42 | 8 | 4.5 | | 100 | 110 | 78(5)* | 326 | 315 | 250(5)* |
| 29D | 2 | 10–23–42 | 10 | 4.5 | 7.39 | 97.8 | 96 | 94(5) | 322 | 296 | 380(5) |
| 51D | 9 | 1–16–43 | 4.1 gm. crystalline Hb | 4.5 | | 51 | 45 | 40(3) | 155 | 138 | 126(3) |
| **Methemoglobin injections** | | | | | | | | | | | |
| 36D | 4 | 12– 8–42 | 7.8 | 4.5 | 7.4 | 36 | 42 | 38(7) | 117 | 134 | 132(7) |
| 62D | 13 | 2–17–43 | 5.5 | 4.5 | 7.45 | 47 | 66 | 69(2) | 126 | 173 | 184(2) |
| 102D | 28 | 5–24–43 | 8.0 | 4.5 | | 67 | 68 | 77(1) | 208 | 212 | 203(1) |
| 104D | 29 | 5–27–43 | 8.1 | 4.5 | | 50 | 63 | 104(1) | 144 | 158 | 368(1) |

* Figure in parentheses denotes number of days after infusion.

merular filtration rate and the effective renal plasma flow; in two experiments, however, the p-aminohippuric acid clearances rose slightly during the infusion. During the period of subsequent observation extending from two to nine days, only insignificant variations from the initial control values occurred. At the end of the experimental period the animals were sacrificed; upon examination of their spleen and liver no pathological lesions were found. It seemed of special significance that pigmented precipitates in the renal tubules were absent. It seems clear that in the acidotic dog the administration of myoglobin fails to produce *any significant impairment of renal*

TABLE II

*Effect of hemoglobin and myoglobin infusions in acidotic dogs*

| EXPERIMENT NO. | NO. OF DOG | DATE OF INITIAL EXPERIMENT | AMOUNT PIGMENT USED | RATE INFUSION | pH OF BLOOD | | UREA NITROGEN | | FILTRATION RATE | | | EFFECTIVE RENAL PLASMA FLOW | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Day of infusion | Follow-up | Day of infusion | Follow-up | Day of infusion: Before infusion | Day of infusion: After infusion | Follow-up | Day of infusion: Before infusion | Day of infusion: After infusion | Follow-up |
| **Hemoglobin injections** | | | | | | | | | | | | | | |
| | | | *gm.* | *cc./min.* | | | | | | | | | | |
| 31D | 2 | 11- 3-42 | 10.0 | 4.5 | 7.14 | | | | 76.0 | 77.8 | 67.60(15)* | 222.0 | 235.0 | 294(15)* |
| 49D | 8 | 1-13-43 | 5.04† | 4.5 | 7.24 | | | | 59.8 | 57.0 | 80.40(1) | 197.0 | 168.0 | 250(1) |
| 53D | 10 | 1-22-43 | 4.8 | 4.5 | 7.29 | | | | 37.5 | 33.7 | 33.80(3) | 104.0 | 109.0 | 97(3) |
| 59D | 11 | 2-10-43 | 5.6 | 4.5 | 7.14 | | 22.0 | 37.5(2)* | 53.0 | 42.0 | 43.00(2) | 185.0 | 180.0 | 200(2) |
| 106D | 28 | 6- 2-43 | 7.0 | 4.5 | 6.90 | | | | 54.0 | 50.0 | 31.00(2) | 193.0 | 182.0 | 117(2) |
| | | | | | | | | | | | 88.00(7) | | | 296(7) |
| **Myoglobin injections** | | | | | | | | | | | | | | |
| 55D | 11 | 2- 2-43 | 4.7 | 4.5 | 7.14 | 7.38(2)* | 16.0 | 17.0(2) | 72.0 | 64.0 | 62.00(1) | 260.0 | 269.0 | 230(1) |
| | | | | | | | | | | | 54.00(2) | | | 193(2) |
| | | | | | | | | | | | 67.00(3) | | | 204(3) |
| | | | | | | | | | | | 104.00(7) | | | 308(7) |
| 64D | 14 | 2-27-43 | 4.7 | 4.5 | 7.18 | 7.40(1) | 17.5 | 18.5(1) | 57.0 | 50.0 | 64.90(2) | 174.0 | 177.0 | 202(2) |
| | | | | | | | | 15.0(2) | | | 71.80(9) | | | 217(9) |
| 67D | 15 | 3-10-43 | 5.8 | 4.5 | 7.13 | | 15.0 | | 56.7 | 49.6 | 44.10(1) | 142.0 | 119.0 | 153(1) |
| | | | | | | | | | | | 40.90(5) | | | 123(5) |
| 105D | 38 | 4-10-43 | 6.1 | 4.5 | 7.10 | 7.40 | | | 65.2 | 60.2 | 64.60(2) | 210.0 | 195.0 | 208(2) |
| 107D | 39 | 6-10-43 | 7.3 | 4.5 | 7.20 | 7.34 | | | 71.0 | 70.8 | 73.20(3) | 248.3 | 230.0 | 255(3) |

* Figure in parentheses denotes number of days after infusion.

† Cryst.

*function.* These results are in agreement with the experiments of Yuile (11), in which the infusion of myoglobin into dogs with normal alkali reserve failed to produce renal failure. They differ, however, from those obtained by Bywaters (10) who demonstrated that the infusion of myoglobin in the acidotic rabbit produced lesions similar in character to those present after crush injuries.

*Effect of methemoglobin*

Since renal failure following blackwater fever is frequently connected with the excretion of methemoglobin (2), it seemed of interest to investigate to investigate the effect of this pigment on the renal function of normal and acidotic dogs. As seen in Table I the infusion of from 5.5 to 8.1 grams of crystalline methemoglobin into dogs with normal alkali reserve resulted in an immediate moderate increase in the clearance values. In the follow-up periods extending from 1 to 7 days, the clearances in three cases showed further slight rises. *Depression of renal function was never observed.* The microscopic examination of the kidneys of these animals revealed normal renal structure, thus confirming the conclusions obtained from physiological data.

The results obtained with methemoglobin in the normal animal contrast sharply with those in acidotic dogs (Table III). In all but two experiments (42D and 70D) the infusion of from 3.31 to 13.5 grams of crystalline methemoglobin produced a decline in the creatinine and the p-aminohippuric acid clearances, usually commencing with the appearance of a dark pigment in the urine, which was spectroscopically identified as methemoglobin. As seen in a typical experiment (Fig. 1) the clearances fell to 10% of their control value. Despite this fall in clearances, the urine flow usually increased at the onset of the pigment infusion, probably because of the diuretic effect of the pigment. In nine out of fifteen experiments this diuresis was succeeded by a rapid decline in the urine flow occurring fifty minutes after the onset of the methemoglobin infusion. In the remaining cases, the urine flow decreased on the second post-infusion day. On the third day the urine flow had dropped to less than 0.2 cc. per minute despite the presence of mannitol in the infusion fluid. The blood pH which ranged from 6.9 to 7.2 at the onset of the experimental

TABLE III

*Effect of methemoglobin infusion in acidotic dogs*

| EXPERIMENT NO. | NO. OF DOG | DATE OF INITIAL EXPERIMENT | AMOUNT PIGMENT USED | RATE INFUSION | pH OF BLOOD | | UREA NITROGEN | | FILTRATION RATE | | | EFFECTIVE RENAL PLASMA FLOW | | | GLUCOSE Tm | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Day of infusion | Follow-up | Day of infusion | Follow-up | Day of infusion | | Follow-up | Day of infusion | | Follow-up | Day of infusion | | Follow-up |
| | | | | | | | | | Before infusion | After infusion | | Before infusion | After infusion | | Before infusion | After infusion | |
| | | | *gm.* | *cc./min.* | | | | | | | | | | | | | |
| 37D | 5 | 12- 9-42 | 7.8 | 4.5 | 7.10 | 7.10(1)* | 20.0 | 75.0(1)* | 70.0 | 33.0 | 21.70(1)* | 243.0 | 124.0 | 5.91(1)* | | | |
| | | | 2.0 | | | | | | | | 0.90(2) | | | 2.15(2) | | | |
| | | | 2.0 | | | 7.10(2) | | 15.0(2) | | | 0.45(3) | | | 0.60(3) | | | |
| | | | | | | 7.13(3) | | | | | | | | | | | |
| 42D | 6 | 12-17-42 | 3.31 | 4.5 | 7.24 | | | | 64.0 | 34.0 | 49.00(1) | 210.0 | 129.0 | 202.00(1) | | | |
| 44D | 4 | 12-22-42 | 7.16 | 4.5 | 7.20 | | 19.0 | 70.0(1) | 38.0 | 25.0 | too low (1)* | 158.0 | 120.0 | too low (1) | | | |
| | | | | | | | | 120.0(2) | | | to be read | | | to be read | | | |
| 46D | 7 | 12-29-42 | 4.7 | 4.5 | 7.05 | 6.90(1) | 15.3 | 75.0(1) | 80.0 | 14.0 | 3.81(1) | 306.0 | 40.0 | 10.3 (1) | | | |
| | | | | | | | | 90.0(2) | | | too low (2) to | | | too low (2) | | | |
| | | | | | | | | | | | be read | | | to be read | | | |
| 70D | 16 | 3-18-43 | 13.5 | 4.5 | 7.26 | 7.38(1) | 27.2 | 17.2(1) | 54.0 | 46.4 | 36.90(1) | 133.0 | 126.0 | 121.60(1) | | | |
| 72D | 17 | 3-23-43 | 9.85 | 4.5 | 6.89 | 7.10(1) | | 17.2(1) | 43.0 | 36.7 | 10.80(1) | 163.0 | 110.0 | 19.00(1) | | | |
| | | | | | | 7.20(2) | | | | | 3.63(2) | | | 4.53(2) | | | |
| 73D | 18 | 3-23-43 | 9.85 | 4.5 | 7.09 | 7.05(1) | | | 48.5 | 34.1 | 4.10(1) | 132.0 | 95.4 | 8.34(1) | | | |
| | | | | | | 7.20(2) | | | | | 0.716(2) | | | 0.32(2) | | | |
| 78D | 19 | 3-31-43 | 7.25 | 4.5 | 7.15 | 7.20(1) | 20.0 | 60.0(1) | 55.7 | 48.7 | 0.207(1) | 130.0 | 96.0 | 3.15(1) | 196.0 | 164.0 | |
| 80D | 20 | 4- 6-43 | 12.8 | 4.5 | 7.14 | 7.16(1) | 16.0 | 42.6(1) | 73.5 | 70.0 | 13.80(1) | 200.0 | 179.0 | 61.50(1) | 230.0 | 231.0 | 50.0(1)* |
| | | | 5.0 | | | 7.20(2) | | 45.5(6) | | | 18.40(2) | | | 48.90(2) | | | 65.0(2) |
| | | | 5.0 | | | 7.35(3) | | 57.9(4) | | | 14.90(3) | | | 36.00(3) | | | 53.0(3) |
| | | | | | | 7.36(4) | | 102.0(5) | | | 14.10(5) | | | 53.30(5) | | | 48.0(5) |
| | | | | | | 7.46(5) | | 170.0(13) | | | 14.20(13) | | | 58.30(13) | | | 56.0(13) |
| 92D | 22 | 4-27-43 | 9.0 | 4.5 | 7.05 | | | | 73.1 | 28.9 | | 258.0 | 35.7 | | 188.0 | 105.0 | |
| 93D | 23 | 4-29-43 | 7.67 | 4.5 | 7.10 | | | | 40.4 | 10.8 | | 164.1 | 40.3 | | | | |
| 94D† | 24 | 5- 4-43 | 8.97 | 4.5 | 7.06 | 7.09(1) | 17.0 | | 83.4 | 73.0 | 3.00(2) | 210.0 | 207.0 | 4.30(2) | 226.5 | 292.0 | 6.4(2) |
| | | | | | | | | | | | 4.13(1) | | | 6.99(1) | | | |
| 97D† | 25 | 5-11-43 | 7.10 | 4.5 | 6.93 | | | | 38.6 | 24.0 | | 71.0 | 45.4 | | | | |
| 98D† | 26 | 5-14-43 | 8.50 | 4.5 | 7.17 | 7.01(1) | | | 126.0 | 36.8 | | 238.0 | 109.0 | | | | |
| 100D† | 27 | 5-17-43 | 12.45 | 4.5 | 6.82 | | | | 63.2 | 46.8 | 1.30(1) | 157.0 | 121.0 | 21.60(1) | | | |

* Figure in parentheses denotes number of days after infusion.

† No mannitol included in sustaining infusion.

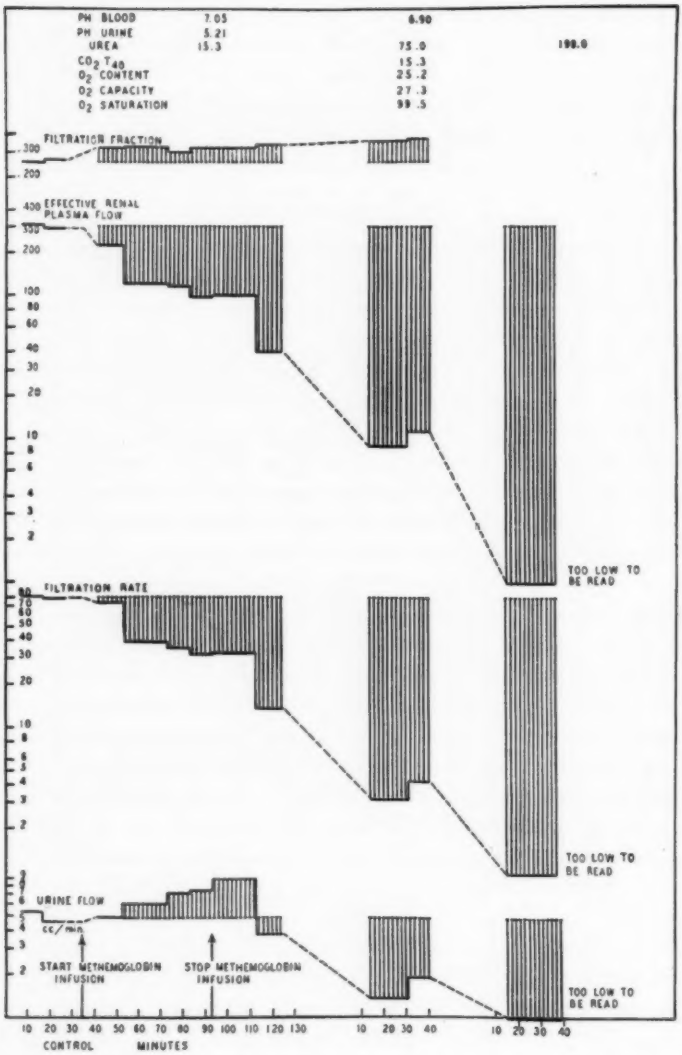


FIG. 1 demonstrates the effect of the infusion of 4.7 gm. of methemoglobin on the renal function of the acidotic dog.

period, remained below normal with the exception of experiment 80D (Table III) in which it rose to 7.46 on the fifth post-infusion

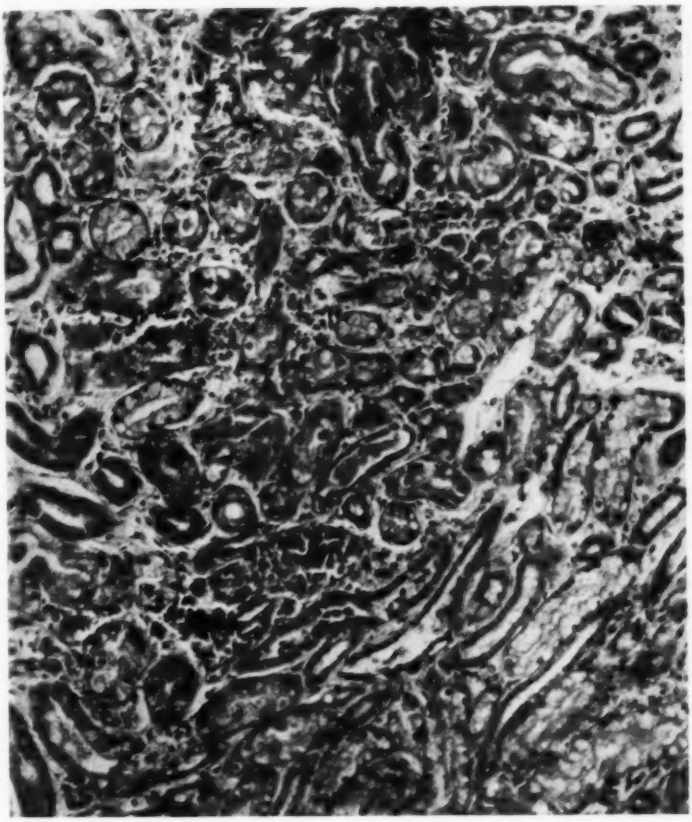

FIG. 2 shows the effect of methemoglobin on the renal structure of the acidotic dog. There are areas of hydropic degeneration of epithelial cells of the proximal convoluted tubules, and of patchy necrosis in the distal tubules. (U. S. Army Medical Museum Reg. No. 77595).

day. In every instance the urine became alkaline on the third day, although the blood pH remained low. A similar observation has been made in cases of renal failure following sulfathiazole intoxication (12).

In all but two cases (experiment 42D and 70D) the blood urea rose markedly on the third post-infusion day (Table III). It seems probable that these two negative results were caused by the high alkali reserve present at the onset of the methemoglobin infusion. It was significant that despite the sharp drop in renal function, none of the urinary specimens revealed pigmented casts. Most animals were moribund on the third day and had to be sacrificed. One animal, however, (80D, Table III), survived for thirteen days, although it had received a total of 22.8 grams methemoglobin, equally divided over a period of three days. During the thirteen-day period the blood urea rose from 16 to 170 mgm. per cent.

In four cases in which methemoglobin was infused, the tubular reabsorptive capacity for glucose (glucose Tm) was followed. As seen in Table III, the glucose Tm fell in every instance following the infusion of the pigment. It is conceivable that this decline was the sequence of afferent arteriolar constriction, preventing the perfusion of a number of nephrons (4). Since the possibility existed that the high concentration of mannitol might be a contributing factor in the production of renal failure, four experiments were performed in which this substance was omitted from the infusion fluid. As seen in Table III, however, this procedure had no influence on the final outcome of the experiments.

Histological examination of these kidneys revealed normal glomeruli. The collecting tubules were plugged with protein material, and some were calcified. The epithelial cells of the proximal convoluted tubules showed hydropic degeneration and desquamation. There were areas of patchy necrosis in the distal convoluted tubules. Pigmented casts were found in the tubular lumina of only two kidneys, from animals which had received three infusions of methemoglobin on successive days (Fig. 2).

### *The effect of acidosis on renal function*

The experiments described above point to the importance of lowered alkali reserve in the production of renal failure. It seemed therefore of interest to study the effect of acidosis in a series of animals which had not received any blood pigment. A series of five experiments were performed in which from 80 to 120 grams of ammonium chloride were



| pH OF BLOOD | $CO_2$ TENSION | $O_2$ CONTENT | $O_2$ CAPACITY | CREATININE CLEARANCE | P-HIPPURATE CLEARANCE | BLOOD LACTIC ACID (MGM. %) |
|---|---|---|---|---|---|---|

*Effect of the intravenous infusions of lactic acid and hydrochloric acid and of oral ingestion of ammonium chloride on renal function of dogs*

| EXP. | NO. OF DOG | DATE OF INITIAL EXP. | AMOUNT ACID INFUSED OR $NH_4Cl$ INGESTED | RATE OF INFUSION | pH OF BLOOD | | $CO_2$ TENSION | | $O_2$ CONTENT | | $O_2$ CAPACITY | | CREATININE CLEARANCE | | P-HIPPURATE CLEARANCE | | BLOOD LACTIC ACID (MGM. %) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Before acidosis | After acidosis | Before acidosis | After acidosis | Before acidosis | After acidosis | Before acidosis | After acidosis | Before acidosis | After acidosis | Before acidosis | After acidosis | Before acidosis | After acidosis |
| **Lactic acid infusions** | | | | | | | | | | | | | | | | | | |
| | | | | *cc./min* | | | | | | | | | | | | | | |
| 6D | 29 | 6–19–42 | 90 cc. 10% | 4.5 | | | 37 | 25 | | | | | 68 | 43 | 188 | 122 | | |
| 7D | 30 | 6–23–42 | 72 cc. 4% | 4.5 | | | 41 | 37 | | | | | 74 | 59 | 208 | 195 | | |
| 9D | 30 | 6–30–42 | 142 cc. 16% | 4.5 | | | 43 | | | | | | 83 | 53 | 283 | 175 | 32 | 60 |
| 11D | 29 | 7– 6–42 | 190 cc. 5% | 4.5 | 7.38 | 7.2 | 42 | 27 | 16 | 14 | 17 | 14 | 58 | 44 | 173 | 128 | 12 | 73 |
| 14D | 30 | 7–20–42 | 100 cc. 5% | 4.5 | 7.41 | 7.1 | 43 | 20 | 17 | 14 | 19 | 16 | 66 | 36 | 214 | 120 | 13 | 179 |
| **Hydrochloric acid infusions** | | | | | | | | | | | | | | | | | | |
| 17D | 1 | 8– 5–42 | 170 cc. .01N | 4.5 | 7.45 | 7.4 | 44 | 45 | | | | | 78 | 79 | 255 | 263 | | |
| 18D | 1 | 8–10–42 | 207 cc. .06N | 4.5 | 7.43 | 7.2 | 50 | 30 | | | | | 79 | 53 | 281 | 166 | | |
| 22D | 1 | 10– 2–42 | 166 cc. .2N | 4.5 | 7.74 | 7.2 | | | | | | | 135 | 74 | 375 | 125 | | |
| **Ammonium chloride infusions** | | | | | | | | | | | | | | | | | | |
| 90D | 22 | 4– 6–43 | 95 g. in 48 hr. | | 7.4 | 7.1 | | | | | | | 61 | 61(1)* | 136 | 158(1)* | | |
| 91D | | 4– 7–43 | | | | | | | | | | | | | | | | |
| 24D | 2 | 10– 6–42 | 80 g. in 72 hr. | | 7.4 | 6.93 | 47 | 16 | 19 | 18 | 20 | 19 | 96 | 84(3) | 335 | 262(3) | | |
| 55D | 11 | 2– 2–43 | 120 g. in 48 hr. | | 7.4 | 7.14 | | 26 | | | | | 77 | 73<br>84(6) | 225 | 260<br>290(6) | | |
| 37D | 5 | 12– 9–42 | 80 g. in 48 hr. | | 7.4 | 7.13 | | | | | | | 76 | 70 | 272 | 243 | | |
| 85D | 21 | 4–14–43 | 100 g. in 48 hr. | | 7.4 | 7.13 | | 30 | | | | | 72 | 43(1)<br>52(2) | 199 | 153(1)<br>190(2) | | |

* Figure in parentheses denotes number of days after infusion.

given by stomach tube over a period ranging from 48 to 72 hours (Table IV). The fall in glomerular filtration rate and the effective renal plasma flow following the ingestion of ammonium chloride was insignificant or absent (Table IV). Two to six days after the ingestion of the salt, clearance values were still normal. It was evident therefore that the oral administration of large doses of ammonium chloride had failed to produce renal damage, a conclusion which was confirmed by the negative histological examination of these kidneys.

The results obtained with ammonium chloride, however, contrasted sharply with those obtained by intravenous infusion of hydrochloric or lactic acid (Table IV), since injection of the latter substance produced a marked drop in clearances. This decline in renal function occurred despite the fact that the values for blood pH were no lower than those observed in the animal which had received ammonium chloride (Table IV). It was especially noteworthy that the fall in clearances coincided with the appearance of a dark brown pigment in the urine which was identified as methemoglobin. Apparently the renal failure following the infusion of acid was caused by the excretion of this pigment which had formed at the point of entrance of the concentrated acid solution into the blood stream.

## DISCUSSION

The experiments dealing with the effect of hemoglobin infusions into the normal and acidotic animal reveal that this pigment is ineffective in producing prolonged renal failure, although slight depressions in the clearance values were observed during the period of infusion and in some instances for two or three days following it.

The negative results obtained with purified hemoglobin are in agreement with those observed by deNavasquez in rabbits (13) and by Ottenberg (14) and others in man. DeGowin and his coworkers (15), on the other hand, observed anuria in a number of their acidotic dogs following hemoglobin injections, and Baker and Dodds (16) produced marked retention of non-protein nitrogen in the blood of rabbits with acid urine by the intravenous injection of this pigment. DeGowin was of the opinion that the anuria was caused by precipitation of hemoglobin by the low urine pH. No explanation for this discrepancy can be found at the present time; but the possibility exists that the

toxic effect of purified hemoglobin observed by DeGowin (15) and by Baker and Dodds (16) might have been caused by the conversion of hemoglobin to methemoglobin in the nephron of their experimental animals.

The infusion of myoglobin into acidotic dogs is equally ineffective in producing renal failure. Both the clearance values and histological examination of kidneys of animals infused with this muscle pigment, failed to demonstrate tubular damage. Bywaters has claimed successful production of renal lesions in the acidotic rabbit by intravenous injection of myoglobin (10). The same author demonstrated also that the renal failure following crush injuries is always accompanied by myoglobinuria (1). The difference in the results of Bywaters and those reported in this paper is possibly caused by variations in the reaction of the test animals, or by differences in the globin fraction of the muscle pigment.

The infusion of methemoglobin into animals with normal alkali reserve does not influence renal function and has no effect on the histology of the nephron. In the acidotic animal, however, methemoglobin infusions produce a fall in clearances which is noticeable either during the infusion period or 24 hours later. The filtration rate, effective renal plasma flow, and the maximal tubular capacity for glucose reabsorption fall to an average of 10% of their control values. The histological picture reveals hydropic degeneration of the cells of the proximal segments, isolated areas of cellular necrosis in the distal tubules, and blockage of tubular lumina with desquamated tubular cells. As in crush syndrome and in transfusion reactions, dilatation of the tubules is absent (3). Precipitation of pigmented casts was only observed in 2 cases. The animals, however, which demonstrate formation of pigmented casts had received repeated infusions of methemoglobin after renal failure had been initated. This fact contrasts with the assumption of deGowin (15) that the formation of tubular hemoglobin casts is an important factor in the production of anuria, since it indicates that the precipitation of pigment is the sequel to, rather than the cause of renal failure.

Two possible explanations suggest themselves for the renal failure observed after methemoglobin infusion, as shown by the fall in clearances and the widespread tubular damage. The fall in the filtration

rate and the effective renal plasma flow might indicate afferent arteriolar constriction, with subsequent tubular damage due to ischemia of the tubular cells. On the basis of this assumption the decline in glucose Tm observed in a series of cases would indicate that the arteriolar spasm is complete, preventing perfusion of the majority of nephrons (4). The observation of Van Slyke and his group demonstrates that severe reduction in the renal blood flow during circulatory failure for a period of hours is often followed by anuria or death of the animal (17). The work of Richards et al. (18), on the other hand, offers a second explanation for the renal failure observed in the experiments reported above. These workers demonstrated an increase in the permeability of the tubules to creatinine following selenium poisoning. On the basis of Richards' experiments the reduction in creatinine and p-aminohippuric acid observed in the experiments described above may not necessarily indicate a decrease in glomerular filtration rate, renal blood flow and tubular reabsorptive capacity for glucose, but could possibly be the result of back diffusion of these substances through the tubular membranes.

A number of conditions have been reported in man, in which the excretion of pigmented urine is followed by anuria and death. In blackwater fever the urine contains methemoglobin (2); myoglobin is excreted during crushing injuries (1); and hemoglobinuria follows both incompatible transfusions and crushing injuries (1, 2, 19). Since methemoglobin has only been demonstrated in the urine of patients suffering from blackwater fever, it is doubtful whether this pigment is the cause of anuria following crushing injuries and incompatible transfusions. It is possible, however, that although the agents differ, the sequence of events consisting either of vasoconstriction or of tubular destruction, followed by blockage with cellular detritus, is identical. The presence of acidosis is also an important requirement for the development of both experimental methemoglobin anuria and the clinical anurias mentioned above. This is indicated by the value of alkalinization therapy in blackwater fever, in crush syndrome, and in mismatched transfusions (3). The role which acidosis plays in the production of these anurias is not clear. It is possible, however, that it exerts its toxic influence in conjunction with methemoglobin through inhibition of respiratory enzymes present in the tubular cells. Experiments are in progress to elucidate this problem.

SUMMARY

1. The intravenous infusion of crystalline methemoglobin into dogs rendered acidotic with ammonium chloride is followed by a fall in the effective renal plasma flow, glomerular filtration rate, and the tubular reabsorptive capacity for glucose.

2. The renal lesion in acidotic dogs infused with methemoglobin consists of hydropic degeneration of the proximal convoluted tubules, cellular necroses in the distal segment and plugging of the collecting tubules with hyaline and in some instances with pigmented casts. Dilatation of the collecting tubules and glomerular damage are absent.

3. Infusions of myoglobin and of hemoglobin into acidotic animals, and of methemoglobin and hemoglobin into normal animals fail to produce renal failure.

4. The intravenous infusion of lactic acid and of hydrochloric acid produces a rapid fall in clearances caused by the urinary excretion of methemoglobin. Acidosis produced by oral administration of ammonium chloride has no effect on the renal function.

5. The mechanism of the methemoglobin anuria and its relation to the etiology of renal failure following blackwater fever, crush injuries and hemoglobin transfusions is discussed.

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# ACUTE DIFFUSE INTERSTITIAL FIBROSIS OF THE LUNGS[1]

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Over a period of two years, from 1931 to 1933, three unusual cases of pulmonary disease were observed upon the Medical Wards of the Johns Hopkins Hospital. All presented puzzling clinical pictures, the exact like of which never before had been noted by members of the medical staff. The symptoms of each case differed somewhat from those of the others and yet bore a striking resemblance so that having seen two cases, the correct diagnosis was suggested when the third appeared. The pathological process in the lungs was identical in all, and this lesion was so extraordinary and distinctive that there can be no doubt that the symptoms displayed by each case, different though they were, arose from the same underlying morbid process, the variation in symptoms depending upon the stage this process had reached at the time the patients came under observation.

We have said that the clinical picture was a new one to the physicians; the anatomical picture was equally unfamiliar to the pathologists. The lungs were the seat of a widespread connective tissue hyperplasia throughout the interstitial structures. The alveolar walls were tremendously thickened; in the early stages of the process crowded with fibroblasts which, at later stages, were replaced by mature scar tissue. It is noteworthy that the alveoli themselves contained little or no cellular inflammatory exudate in contrast with what is seen in pneumonia. These pulmonary changes caused an extreme degree of dyspnoea and cyanosis, and after a matter of only a few weeks, led to dilatation and hypertrophy of the right ventricle of the heart so that at the end, in the one patient who survived the earlier stages of the disease, grave symptoms of myocardial insufficiency developed.

[1] The observations here reported were used by one of the authors (L. H.) as the material of the Mellon Lecture, delivered before the Society for Biological Research, at Pittsburgh, May 27, 1943.

In 1935, at the meeting of the American Clinical and Climatological Association (7), we briefly reported these observations, adding a fourth case we had observed only a few months before. In this patient, the illness had run a fulminating course, for death had occurred three days after the onset of symptoms. At the post-mortem examination, throughout both lungs the alveoli contained albuminous fluid and red cells with few leucocytes; the alveolar epithelial cells were greatly enlarged; a hyaline membrane lined some of the alveoli; the alveolar walls were edematous and contained fragments of fibrin, a few mononuclear cells and an early proliferation of fibroblasts. No organisms grew in cultures from the lungs. We thought at the time, and still think, that the changes found in the lungs probably represent early lesions of the condition under consideration. Nevertheless, there is no assurance that this view is correct and we prefer, therefore, to omit the case from the present report.

In the discussion that followed our report, Dr. Willard B. Soper and Dr. William P. Finney each referred to a patient they had observed with symptoms resembling those of our patients. At the post-mortem examinations, the microscopical study of sections of the lungs had revealed the same changes that we had described. Dr. Finney had submitted his specimens to Dr. William G. MacCallum who said he had never before seen anything quite like them. Dr. Milton C. Winternitz had examined the specimens of Dr. Soper and had said that the changes there observed were new to him, but added that they bore a striking resemblance to what he had found in the lungs of animals during his experimental investigations on influenzal pneumonia. A little later, Dr. Russell L. Haden sent us a brief report of the clinical features and autopsy findings of a patient he had observed in 1916. Fortunately, the microscopical preparation of a section of the lung had been preserved and this section he sent with the report. A study of the section revealed thickening of the alveolar walls, but the alveoli were plugged with living and dead lipoid-laden macrophages and contained many crystals, apparently cholesterol. It seems that the pulmonary changes in this case may have been caused by the aspiration of some irritating lipoid material. We delayed publishing a full report of our observations, confidently expecting that we would discover many more instances of the disease. However, to our sur-

prise and disappointment, ten years passed without our seeing another, and only last April did the fourth case come to autopsy.

CASE 1

Unit History No. 40726. A colored man, married, forty-seven years of age, came to the hospital December 16, 1931, complaining of cough, shortness of breath and swelling of the ankles. He was a laborer and had always done hard work. He had had pneumonia in 1912 from which he had fully recovered and apparently had not had cough nor shortness of breath before the onset of his final illness. He had had a gonorrheal infection in early manhood. In 1917 he had been treated with injections into the arms and hips, no doubt for a syphilitic infection.

Three weeks before admission the patient had caught cold and had had a dry, harassing cough and three or four days later had developed a small amount of mucopurulent sputum. He was not ill enough to be in bed and kept at his work. Ten days before admission he had noticed that he was becoming very short of breath on exertion. His cough had continued and the shortness of breath had become increasingly worse. Eight days before admission he had given up work and had rested at home. On the day that he came into the hospital he had again tried to work but had become so short of breath that after a few hours he had been obliged to stop. His ankles had been swollen for a week.

*Examination.* Temperature 101.4°; pulse 84; respiration 36; blood pressure, systolic 130, diastolic 100.

He was well developed, well nourished, in moderate respiratory distress. He was able to lie flat without extreme dyspnea. He had a dry, brassy cough with a small amount of mucoid sputum. The mucous membranes had a good color. The eyes were normal excepting an arcus senilis. Pupils were equal, reacted actively. The fundi showed moderate arteriosclerotic changes. Teeth were in very bad condition. Throat showed nothing remarkable. The chest was broad and rounded and moved somewhat as a whole. The percussion note over the lungs was resonant except for some impairment over the left lower lobe. Breath sounds everywhere were harsh, expiration prolonged, and very numerous fine and coarse moist rales were heard all over the chest, more marked over the lower front and back than over the upper portions. The apex beat of the heart was in the fifth interspace a little to the left of the mamillary line. The area of cardiac dullness was enlarged, measuring four and a half centimeters to the right and eleven and a half centimeters to the left of the midline. There was no unusual pulsation over the heart. The veins in the neck were engorged and pulsated prominently. Heart sounds were distant and muffled; a systolic murmur was heard at the apex. The heart seemed to move satisfactorily with change of position. The pulse was regular, rapid, equal at the two wrists. Blood pressure, however, was a little higher in the right arm than in the left, although this observation varied from time to time. The peripheral vessels were tortuous and considerably thickened. The abdomen was distended. The liver extended three finger-breadths below the

costal margin. The spleen was not felt. Genitalia showed nothing abnormal. The neurologic examination was negative. There was moderate pitting edema over the legs up to the knees and over the sacrum.

*Course in the hospital.* On admission to the hospital the patient was given digitalis and the edema diminished. The pulmonary signs persisted. The temperature remained elevated, varying between 99.6° and 103° for a period of two weeks. It then gradually fell but for a long time there were occasional elevations to 99° and 100°. Respirations were rapid and somewhat labored. With the fall of temperature, there was improvement in the pulmonary signs, the rales becoming less numerous and the sputum decreasing. The patient, too, felt much more comfortable. At the end of a month very marked ascites developed, somewhat out of proportion to the amount of subcutaneous edema. The fluid withdrawn by puncture had the characters of a transudate. A few weeks later the edema again was more marked. There was general anasarca. The pulmonary signs had cleared to a large extent so that moist rales were heard only at the bases. Throughout the period in the hospital cyanosis was always extreme. The blood showed a percentage oxygen saturation of sixty, later of fifty. From the middle of February on the patient grew slowly but steadily worse. The dyspnea and edema became more marked, there was extreme cyanosis and, from time to time, wandering delirium. The heart apparently had become somewhat more enlarged because at the end of February the note was made that the apex beat was in the sixth interspace. An area of necrosis of the jaw bone developed about an infected tooth. The patient died of heart failure on March 22, 1932.

*Laboratory examinations:*

Blood count:

| | Hgb. | Red blood cells | White blood cells |
|---|---|---|---|
| 12/16/31 | 101% | 4,300,000 | 10,760 |
| 2/21/32 | 93% | 5,360,000 | 8,760 |
| 3/15/32 | 100% | 5,980,000 | 7,200 |

Wassermann reaction: Positive.

Blood chemical studies:

| | NPN mg. per 100 cc. | van den Bergh | Total prot. (per 100 cc.) gm. | A/G rat. | $CO_2$ vol. per cent | NaCl per 100 cc. mg. |
|---|---|---|---|---|---|---|
| 12/17/31 | 58 | trace | | | | |
| 12/22/31 | 40 | trace | | | | |
| 1/11/32 | 39 | trace | 5.6 | 43/57 | | |
| 1/20/32 | 24 | trace | 4.86 | | | |
| 1/25/32 | | | 5.61 | 38/62 | 52 | 488 |
| 2/13/32 | 76 | trace | | | | |
| 2/15/32 | 48 | trace | | | | |

Jan. 6. Oxygen content, 13.57 vol. per cent. Oxygen capacity, 20.32 vol. per cent. Percentage oxygen saturation, 67.

Feb. 11. Oxygen content, 10.3 vol. per cent. Oxygen capacity, 20.6 vol. per cent. Percentage oxygen saturation, 50.

Sputum: Tenacious, mucopurulent, occasionally blood streaked. Many and prolonged searches for tubercle bacilli all were negative.

Blood cultures: No growth.

Ascitic fluid: Straw colored, specific gravity, 1.005; a few red blood cells and leukocytes in the sediment. Guinea-pig inoculation negative for tuberculosis.

Urine: Specific gravity varied from 1.010 to 1.030. Always contained a large amount of albumin and many hyaline and granular casts.

Temperature during the first two weeks varied from 99.6° to 103°; then for two or three weeks was at a lower level and later hovered about normal, occasionally going as high as 100°.

Blood pressure: The systolic varied from 142 to 90 mm. Hg.; the diastolic from 100 to 60.

Roentgenograms:

12/17/31. Tele.: M.R. 5.0; M.L. 8.8; A. 5.5; T. 26.1.
Chest: Enlarged heart. Changes in both lungs probably secondary to cardiac condition. No aneurysm seen.
Abdomen: L. spine negative; exostosis on both ilia.

12/21/31. Chest: Heart and aorta enlarged. Some chronic passive congestion at bases. Very diffuse miliary infiltration both lungs, with little thickening of pleura along axillary border of lung but no fluid; lung changes probably due to miliary tuberculosis with dilated heart and aorta.

1/8/32. Tele.: M.R. 7.2; M.L. 10.2; A. 5; T. 29.
Chest: Very definite dilatation of heart. Chronic passive congestion of lungs, also some changes in lungs which suggest tuberculosis, in addition to chronic passive congestion. Some thickened pleura over R. chest.

2/1/32. Chest: Cardiac shadow markedly enlarged, with some dilatation of aorta. Infiltration of both lungs with pleurisy at right axillary line. Lung changes probably secondary to cardiac condition.

Electrocardiograms:

12/17/31. Normal sinus rhythm. T III inverted. Dextrogram.

12/31/31. Normal sinus rhythm. T I biphasic. Dextrogram.

1/5/32. Normal sinus rhythm. T III inverted, otherwise no change since last record.

2/1/32. Nodal rhythm suggesting overdigitalization. Dextrogram. T wave inverted in all leads.

2/8/32. Rhythm still originates in A-V node. There is a shift of 15½ of the electrical axis on change of position.

3/2/32. Rhythm totally irregular. No regularly spaced P waves. Auricular fibrillation probably, although there is no definite evidence of auricular activity. T waves inverted in all leads.

3/22/32. Rhythm arises at A-V node. T I and II upright. T III inverted. Slurring of QRS complex in all leads suggests myocardial damage.

The authors have published this case as a clinical pathological conference (8), and there discuss in detail the diagnostic problem and the character and significance of the lesions found at autopsy. The patient excited the liveliest interest during his stay upon the ward, and even to the present day the memory of his illness is constantly recalled by the medical staff and kept alive in clinical discussions. Indeed his name has become the familiar term used to epitomize the characteristic features of the disease we are now describing.

It is quite clear from the summary of the clinical records that the outstanding feature of the illness was the increasing evidence of myocardial insufficiency. When the patient entered the hospital the heart was enlarged and he had dyspnea and edema; later the edema became very pronounced and there developed intense cyanosis and great engorgement of the veins; finally, he died of heart failure. It is important to bear clearly in mind the predominance of the cardiac symptoms, for these were the late manifestations of what was at first an acute pulmonary inflammation. At the time of admission to the hospital the patient had cough and fever and the examination disclosed the unmistakable signs of scattered areas of consolidation throughout the lower lobes of the lungs. These signs gradually receded as the symptoms of a failing circulation increased and finally only râles of edema remained over the lower lobes. The patient stated that he had been perfectly well and hard at work without cough or dyspnea until three weeks before he entered the hospital.

The diagnostic difficulties must at once be apparent. When the patient came to the hospital the presence of fever and scattered areas of pulmonary consolidation suggested that he had bronchopneumonia. However, acute bronchopneumonia seemed not to explain the enlargement of the heart and the obvious symptoms of myocardial failure. Later, when ascites became prominent, the possibility of tuberculosis was considered, that is, tuberculosis of the lungs, pericardium and peritoneum. This diagnosis was abandoned when increasing evidence yielded no support for it. The fever fell, the peritoneal fluid had the characteristics of a transudate, the signs of pulmonary consolidation

receded, and tubercle bacilli could not be found in the sputum nor in the ascitic fluid by microscopic search and animal inoculation.

As the disease progressed the great enlargement of the right side of the heart, as seen in the teleoroentgenogram and demonstrated by the electrocardiograph, and the signs of predominant weakness of the right ventricle, namely, massive edema, venous engorgement and extreme cyanosis, forced the conclusion that the heart had enlarged and at last failed as a result of hypertension in the pulmonary circulation. The apparently short duration of the illness, the absence of any pulmonary symptoms until three weeks before the admission of the patient to the hospital, and the gradual diminution of the signs of consolidation led to the final prediction that the cause of the hypertension was sclerosis of the pulmonary arteries.

As will be seen in the pathological report, the post-mortem examination revealed the most extensive fibrosis of the lungs. However, previous clinical experience had given little reason to believe that great enlargement of the heart and heart failure could follow so shortly upon the development of increased pressure in the pulmonary circulation. When the patient entered the hospital, three weeks after the onset of symptoms, the heart was already enlarged, the liver swollen and there was edema of the legs. He died of heart failure four months after the beginning of the illness. At the time the patient was under observation we had never before witnessed clinically so rapid a march of these events. It was difficult to believe that the heart could enlarge to the degree which was present during the brief space of three or four weeks. Nevertheless, later observations leave us with little doubt that actually this may take place.

At autopsy (No. 12505) both *lungs* were found to be covered with fibrous adhesions which bound the organs to the chest wall and obliterated both pleural cavities. On section, there was seen a close network of very fine, translucent gray scars in all lobes of both lungs from apices to bases. This fine, web-like, diffuse fibrosis was visible on the cut surfaces of all of many parallel sections made throughout the substance of both lungs. There were no large scars. Many focal areas of emphysema were associated with the scars. (Fig. 11.) The macroscopic bronchi were not dilated. There was a small encapsulated calcified nodule in the middle lobe of the right lung, calcified nodules in the hilar nodes, and a scar beneath the pleura at the apex of the right lung. The pulmonary arteries and veins contained no thrombi.

Microscopically the pleural adhesions were fibrous, with no suggestion of tuberculosis. Sections made from all lobes of both lungs showed essentially the same picture. Interlacing bands of fibrous tissue, fully formed and in places hyalinized, cut across the sections in all directions, replacing much of the lung substance (Fig. 12). Nowhere was the process of fibrosis in progress. Some of the scars contained numerous mononuclear cells, and there was also a scattering of eosinophils. There was nothing specific about these scars; nothing that suggests what the etiology may have been. No residue of anything suggestive of tuberculosis was associated with the scars; there was no excess of coal pigment or of other foreign particulate matter. The alveoli between the scars were often emphysematous, though there were areas where they were normal. The emphysema doubtless represented that which is commonly associated focally with scars in the lung, and is due in part to constriction of terminal bronchioles by the scars. Such bronchiolar constriction was present in the sections of these lungs. There was slight intimal thickening of occasional branches of the pulmonary arteries, but nothing in any way comparable to a primary, diffuse obliterative pulmonary endarteritis. Numerous alveoli contained "heart-failure cells" (haemosiderin-laden macrophages). There were minute foci of fresh, terminal pneumonia.

The *pericardial cavity* was practically completely obliterated by fibrous adhesions, which were non-specific macroscopically and microscopically. Some adhesions on the external surface of the pericardium were loosely continuous with the pleural adhesions.

The *heart* had a rather globular shape and was very little enlarged. The enlargement was confined to the right side. The right auricle was somewhat dilated. The right ventricle was only slightly dilated, but its wall was markedly hypertrophied, measuring 1 cm. in thickness. The left auricle was normal in size. The left ventricle was neither dilated nor hypertrophied. It measured 15 mm. in thickness. All of the valves were normal. The myocardium was normal grossly and microscopically. The coronary arteries were slightly sclerotic.

The *aorta* was not dilated, and there was no macroscopic or microscopic evidence of syphilis.

The only other pertinent findings at autopsy were subcutaneous edema, 300 cc. of clear, amber ascitic fluid (there was a fresh paracentesis wound through which fluid had been withdrawn shortly before death), and marked visceral chronic passive congestion.

In this case, the period of active connective tissue formation in the lungs was well passed at the time of autopsy; and the diffuse, non-specific scar tissue that remained provided no clue, either in its histological character or in its location, regarding the nature of the process which had resulted in its formation. Since the pleural and pericardial cavities were obliterated by fibrous adhesions, it was first thought that

the entire process might represent the end result of a pyogenic infection of the lungs and adjacent serous cavities. However, such a universally diffuse, fine fibrosis throughout all lobes of both lungs must be a very rare sequel of bacterial pneumonia, if, indeed, it ever occurs; and in the light of the succeeding cases we regard it as altogether probable that this case represents a late stage of the peculiar interstitial pulmonary fibrosis exemplified by the succeeding cases, rather than the result of a banal, organizing pneumonia.

The patient's symptoms are well enough explainable by the pathological findings. The diffuse fibrosis obviously entailed a great reduction of the functional alveolar capillary bed and of alveolar space, and the vascular bed was further reduced by the many foci of emphysema. These changes, in themselves, could be sufficient to cause dyspnea and cyanosis. In addition, the elevation of the pressure in the pulmonary artery resulting from the reduction of the pulmonary vascular bed placed a burden upon the right ventricle, leading to its hypertrophy and eventual failure. The anoxaemia resulting from the extensive pulmonary alterations may well have been a contributory factor in the production of the heart failure, for deficient oxygenation of the blood is well known to have a deleterious effect upon the myocardium.

It is necessary to comment upon the fact that although the heart was described as being enlarged clinically, it was not appreciably enlarged at autopsy. Indeed, the adhesive, fibrous pericarditis had served to restrict the dilatation of the heart to the degree that there was not even the amount of dilatation of the right ventricle that the pulmonary condition would have led one to suspect. This interference with compensatory dilatation may, itself, have been a factor in contributing to the failure of the heart. It seems probable that the cardiac enlargement noted clinically may have been only apparent. It was noted when the ascites was reaching its maximum, and it is well known that elevation of the diaphragm caused by ascites shifts the apex to the left and produces an apparent enlargement of the heart.

### CASE 2

Unit History No. 41479. A young colored woman, twenty-one years of age, came to the Accident Room of the hospital on July 23, 1928, with a knife wound of the abdominal wall. The wound was dressed and she was given tetanus antitoxin.

No further observations were made. On January 18, 1932, she came to the Gynecological Clinic of the Outpatient Department complaining of profuse, prolonged menstruation and weakness. A diagnosis of myomata uteri was made and operation advised. On January 29, 1932, she was admitted to the hospital and on February 2 was operated upon. Hysteromyomectomy, appendectomy and salpingo-oophorectomy, right, were performed. In addition to the pelvic condition, the following abnormalities were noted. The blood pressure was systolic 152, diastolic 104. The Wassermann reaction on the blood serum was positive. The tonsils were infected. The heart and lungs are reported to have been normal. A lumbar puncture yielded clear fluid under normal pressure; the Wassermann test and the colloidal mastic test were negative. The urine was normal. The patient made an uneventful recovery and left the hospital on February 19, 1932, in good condition. Thereafter she returned regularly to the Gynecological Clinic complaining often of weakness and occasionally of chilliness and pain in the chest. During the same period she received arsphenamine treatment in the Syphilis Clinic of the hospital and later at the City Clinic. The blood pressure was taken once during this time and registered systolic 138, diastolic 90. On July 25, 1932, she was examined at the Gastro-Intestinal Clinic. She complained of poor appetite, constipation and indigestion. The diagnosis made was splanchnoptosis, gastric neurosis, surgical menopause. The blood pressure was systolic 160, diastolic 118. At a return visit on August 30, she complained of a chest cold which she had had for eight days. On October 4, 1932, she was seen at her home by the hospital extern. She stated that she had had shortness of breath for two weeks coming on at first with exertion and growing rapidly so severe that she soon had been obliged to remain propped up in bed. The extern made the provisional diagnosis of myocardial failure and the patient was sent at once to the hospital. The history there obtained was unsatisfactory and, in many details, contradictory. Apparently, the final illness had begun sixteen days before admission to the hospital, with shortness of breath that came on at the end of a strenuous day. Soon the dyspnea was so severe that she had been obliged to remain in bed. Two days later she had called in a physician, who, finding her propped up in bed with marked dyspnea and slight edema of the ankles, prescribed digitalis. At the time of his visit she had had no fever. The lungs, he stated, had been clear. The patient had gotten some relief from the treatment. Two days before admission a severe pain had come on in the left axillary area, made worse by deep breathing, and she had developed slight cough and fever. The husband stated that the patient never had been "real well" after the operation in January. She had been weak, had lost weight and had had one cold after another. He did not confirm the statement that the illness had begun with conspicuous dysnea.

*Examination.* Temperature 101°; pulse 120; respirations 72; blood pressure, systolic 165, diastolic 110.

The patient was a sparely nourished colored woman, propped up in bed with marked dyspnea and tachypnea. She coughed frequently raising small amounts

of greenish, mucopurulent sputum. She complained of pain over the lower part of the left side of the chest. There was only moderate cyanosis. The eyes were normally prominent; pupils equal and reacted actively. The teeth were in fairly good condition but there was infection of the gums. The throat showed nothing remarkable except that the tonsils were large, scarred and ragged. A few of the cervical lymph nodes were palpable, also the axillary and inguinal nodes and one epitrochlear. The excursion of the chest was everywhere limited but it was especially restricted over the lower part of the left side. The percussion note over the lungs was impaired over the left upper front to the fourth rib and over the left upper back to the angle of the scapula. There was dulness also at the left base. The breath sounds over the areas of dulness were high pitched and about the angle of the scapula, bronchovesicular in quality. Numerous moist rales were heard over the lower left front and at both bases behind. The heart was somewhat enlarged, the area of dulness measuring 3 cm. to the right and 11 cm. to the left of the midline. A well marked diastolic shock was felt in the pulmonary area. At the apex was heard a loud systolic murmur. The pulmonary second sound was accentuated. There was protodiastolic gallop rhythm. A friction rub was heard near the heart, probably a pleuropericardial friction. The pulse was rapid, regular. The vessel walls were not thickened. The abdomen was distended. The liver extended one finger breadth below the costal margin. There was no edema of the extremities. The pelvic examination revealed no important abnormality. The reflexes were hyperactive.

*Course in the hospital.* The patient was desperately ill on admission and the following day she was worse. The breathing was perhaps a little easier but she was more deeply intoxicated and the cyanosis was more pronounced. Evidence of consolidation appeared on the right side in addition to that on the left. At one time she became almost pulseless and the blood pressure could not be read. On the second day she was distinctly better. As long as she remained in the oxygen tent she looked fairly well but as soon as taken out she became intensely cyanotic. On the day after admission the temperature varied from 101° to 102°, on the third day it fell to normal and thereafter varied from 98° to 102°, on the third day it fell to normal and thereafter varied from 98° to 100°. The signs of consolidation on the two sides persisted, indeed they extended. She was always cyanotic, often delirious. Respirations were grunting. The sputum became typically rusty. The manifestations of infection subsided but the consolidation in the lungs persisted as did also the dyspnea and cyanosis. A loud pleural friction developed over the right lower front and back. The condition of the heart changed but little. The impulse was forcible, the sounds loud, the second pulmonic sound accentuated. The systolic murmur persisted at the apex. The pulse became quick, almost collapsing in quality, and a capillary pulse was seen in the nails. No diastolic murmur was ever heard. At the end of two weeks the patient was generally somewhat better as long as she remained in the oxygen tent. She had eaten little and lost weight. She had little cough and there seemed to be some recession of the signs of pulmonary infiltration and pleurisy. At the end of three weeks she was

out of the oxygen tent for forty-eight hours to permit estimation of the oxygen saturation of the blood. During this period she was comparatively comfortable though always very short of breath and cyanotic. However, the dyspnea again increased and she could not bear even a short period out of the oxygen tent. Finally her pulse became more rapid and feeble and she died thirty days after entering the hospital and forty-six days after the onset of her final illness.

*Laboratory examinations:*

Blood count:

10/4/32. Hgb. 95%; red blood cells 4,700,000; white blood cells 9,950.
Differential Count:
Polymorphonuclear neutrophiles, 85%.
Polymorphonuclear eosinophiles, 1%.
Polymorphonuclear basophiles, 1%.
Lymphocytes, 11%.
Monocytes, 2%.
Smear: No anisocytosis or poikilocytosis. No marked central achromia. No basophilic stippling.

10/5/32. White blood cells 12,900.

10/11/32. Hgb. 70%; red blood cells 4,460,000; white blood cells 7,550.

10/29/32. Hgb. 106%; red blood cells 5,020,000; white blood cells 15,000.
Differential Count:
Polymorphonuclear neutrophiles, 85%.
Polymorphonuclear eosinophiles, 2%.
Polymorphonuclear basophiles, 0%.
Lymphocytes, 9%.
Monocytes, 4%.

Blood cultures:

10/5/32. No growth after seven days in broth or on dextrose or plain agar plates.

10/13/32. No anaerobic growth. No growth on dextrose ascitic broth or dextrose blood agar in 10% $CO_2$ atmos.

10/14/32. Agglutination for tularemia: No agglutination with B. tularense.

Culture from sputum: 10/15/32. Staphylococcus aureus (nonhemolytic) A. strep.

Culture, lung and pleura: 11/3/32. No aerobic or anaerobic growth.

Sputum: 10/26/32. Thin, mucoid material with no gross blood or particles. No tubercle bacilli found.

Blood chemical studies:

10/26/32. Nonprotein nitrogen 36 mg. per 100 cc.

10/29/32. $CO_2$ 51.3 vol. per cent.

Urine: Specific gravity ranged from 1.008 to 1.020. Occasionally a slight trace of albumin and on two occasions a slight trace of sugar. Micro: Many white blood cells; no red blood cells or casts.

Oxygen saturation: 10/26/32:
Venous blood.
Oxygen content 6.28 vol. %.
Oxygen capacity 17.1 vol. %.
Oxygen saturation 36.8%.
Arterial blood:
Oxygen content 10.43 vol. %.
Oxygen capacity 19.05 vol. %.
Oxygen saturation 54.8%.
Roentgenograms:
10/5/32. Chest: Extensive pneumonia both lungs.
10/8/32. Chest: Examination not satisfactory because patient cannot hold breath; evidently bronchopneumonia each lung; no material change has taken place in appearance of lung since previous examination.
10/15/32. Chest: Large areas of pneumonic consolidation each lung; impossible to make any comparative reading of last films because examinations were unsatisfactory due to the fact that patient cannot hold breath.
10/19/32. Chest: Both lungs involved by extensive process; does not have all characteristics of pneumonia; indicating that there is some pulmonary edema associated with this pneumonia.
Electrocardiograms:
10/14/32. Rate 91. Rhythm—sino-auricular. P-R interval .17. QRS duration—normal. Normal sinus rhythm. T III biphasic.
10/29/32. Rate 125. Rhythm—sino-auricular. P-R interval .17. QRS duration—normal. Normal sinus rhythm. Sinus tachycardia. T waves inverted in all leads.
The temperature ranged from 98° to 102.8°.
The pulse ranged from 68 to 144.
The blood pressure on admission was systolic 160, diastolic 110; later it varied from systolic 160 to 110, diastolic 90 to 80.

There is ample reason for the belief that the story of the onset of the illness as given by the patient is vague and undependable. Nevertheless, it does seem clear that there was no abrupt, clearly defined beginning of the symptoms and that gradually increasing dyspnea was the outstanding manifestation. Indeed, to read the history prepares one to anticipate heart failure rather than pulmonary disease. The examination revealed areas of consolidation in the left lung, a little later also in the right lung and these signs persisted throughout the illness. Fever was inconspicuous, cough and expectoration were slight and the

evidence of intoxication was not striking. In a word the usual clinical picture of pneumonia was not portrayed. Instead, as we have said, dyspnea and cyanosis dominated the picture. Dyspnea was especially prominent and of a peculiar sort. The patient breathed very rapidly with shallow inspiration and quick grunting expiration. She was literally panting. There was little doubt that the great respiratory distress was occasioned by a gradual diminution of alveolar space, the result we thought, of a slowly organizing pneumonia. When the patient first came under observation the possibility of tuberculosis was seriously considered but the course of events failed to confirm or even support this diagnosis.

Although finally all were convinced that the symptoms were due in very large measure, if not entirely, to organizing pneumonia, still the condition of the heart was a perplexing problem. The symptoms at onset were similar to those of beginning heart failure, and the fact that the heart was enlarged and that a definite gallop rhythm was heard indicated clearly that the heart was not normal. Therefore, although all agreed that the shortness of breath was chiefly pulmonary, still, it was thought by most that heart weakness was partly responsible for the peculiarly rapid, panting breathing. The cause of the cardiac enlargement was obscure, but was thought to be due to hypertension even though the evidence of long-standing hypertension was very meagre. Early in 1932, eight months before the beginning of the fatal illness the blood pressure had been, systolic 152, diastolic 104, and at a visit to the hospital two months before, systolic 165, diastolic 118. However, during the interval between these observations the blood pressure was recorded once, upon which occasion it was systolic 138, diastolic 90.

At autopsy (No. 12848) all lobes of both *lungs* were largely occupied by firm, gray and pinkish-red areas of considerable size. Between these extensive areas of solidification there were thin zones of more normal, air containing tissue. There were no definite macroscopic scars. The pleurae were slightly granular (Fig. 1).

The *heart* weighed 350 grams. The epicardium was smooth. The right ventricle was distinctly hypertrophied, measuring 6 mm. in thickness. It was somewhat dilated. The left ventricle was normal in size. It measured 15 mm. in thickness. The valves were normal. The coronary arteries were normal. The myocardium was normal grossly and microscopically.

The *aorta* was normal.

The only other pertinent findings were small amounts of fluid in the pleural and pericardial cavities, and visceral chronic passive congestion.

The culture of the left lung was sterile; that of the right lung contained a widely mixed flora, consisting of about ten different organisms—apparently the result of terminal aspiration of infected material. The post-mortem blood culture was sterile.

The histological characteristics and the manner of development of the pulmonary lesions of the condition under discussion are revealed with especial clarity in this case, for here one can find virtually all stages of the process, from the acute inflammatory phase to completed fibrosis. It is quite clear from the pathological study of this case, as, indeed, it was from the clinical study, that the attack on the lungs in this condition does not begin everywhere at once but, rather, spreads from place to place until all lobes of both lungs have become diffusely involved with lesions in different stages of development. In this case, while some of the lesions were densely scarred, others were so fresh that it was obvious that the patient had died while the causative agent, whatever it may be, was still active.

The earliest lesion appears to consist in a marked dilatation of the capillaries in the alveolar walls and an exudation of fluid into the walls and alveoli. The walls are, therefore, edematous and swollen. Shreds of fibrin are found within them, and fibrin clots the exudate that escapes into the alveoli. There is a decided tendency to the formation of a thick, hyaline membrane of inspissated fibrin, which lines the alveoli. (Figs. 2, 3, 5, 6.) Cellular exudation is sparse, and is limited to a few polymorphonuclear and mononuclear cells in the alveoli and in their walls. Hemorrhage into the alveoli from the dilated capillaries is common. The epithelial cells that line the alveoli are markedly swollen, and some are necrotic. (Fig. 3.) No inclusion bodies are seen, and no stainable bacteria are present. Some of the bronchioles have lost their epithelium and are lined by a hyaline membrane or relined by flat, regenerated epithelium.

The next stage of the process is marked by the appearance of large fibroblasts within the edematous alveolar walls (Figs. 2, 3), and the progressive proliferation of the fibroblasts until the walls become very much thickened (Figs. 5, 6). Mononuclear inflammatory cells

also increase in number in the walls; there is a scattering of eosinophils; and there is a new formation of capillaries (Fig. 4). Where the hyaline membrane that lines the alveoli rests against the wall at sites at which the lining epithelium has been lost it often becomes invaded by fibroblasts from the wall and becomes incorporated into the wall, adding to the latter's thickness.

It is particularly striking that, in spite of the remarkably active proliferation of fibroblasts within the alveolar walls, there is very little organization of the exudate within the alveoli (Figs. 5, 6). Here and there the intra-alveolar hemorrhage or fibrin undergoes organization, but this is far less conspicuous than the organizing process within the alveolar walls. In this, the condition differs strikingly from an ordinary organizing pneumonia, in which the alveoli become plugged with a new growth of connective tissue while most of the alveolar walls undergo little organization. We wish to lay particular stress upon this difference, for the essential peculiarity of the condition under discussion is the remarkable proliferation of connective tissue that occurs within the alveolar walls, even in the absence of organizing exudate in the related alveolar spaces. It is this primary localization of the organizing process which has led us to designate the condition as "interstitial fibrosis."

In the later stages of the process the newly formed interstitial connective tissue becomes mature (Figs. 7, 10, 12), and the alveolar walls appear as thick septa rich in connective tissue. In foci where the organizing process involves intra-alveolar exudate as well as the alveolar walls, the architecture of the lung may become altogether obliterated and replaced by scars. In the areas of more advanced involvement, numerous small branches of the pulmonary artery show an intimal proliferation that narrows the lumen considerably. In numerous places bronchial epithelium has spread from terminal bronchioles to line adjacent alveoli, sometimes assuming a squamous character. Some of the terminal bronchioles are stenosed by surrounding connective tissue, leading to emphysematous dilatation of associated alveoli. There is an inconspicuous scattering of mononuclear cells in the walls of some of the bronchioles, but this is trivial, and nowhere approaches the degree of infiltration familiar in interstitial bronchopneumonia.

CASE 3

Unit History No. 51614. A colored woman, thirty-seven years of age, was admitted to the hospital on October 6, 1933, complaining of shortness of breath and aching in the interscapular area. Nine years before, in June, 1924, she had registered at the Syphilis Clinic. Her husband was under treatment for syphilis and two children were being treated in the Harriet Lane Home for congenital syphilis. The patient came at that time not because she was ill but because she was requested to do so by the visiting nurse. The physical examination was quite negative except that there was some dulness above the right clavicle. She was treated for a time and then disappeared. On October 6, 1933, she came again to the Outpatient Department and being quite ill was at once admitted to the hospital. There she stated that she always had been in good health. She had worked hard, mostly in the fields. In the summer of 1932 she had coughed up a cupful of bright red blood. Shortly before her final illness she had gone to the Dispensary at Sparrows Point where she had received seven or eight intravenous injections. Eleven days before coming to the hospital, which was a day or two after she had received an injection, while picking beans in the field, she was suddenly taken with severe pain in the interscapular area. She did not stop her work immediately and suffered a great deal of pain throughout the day. That night when she got into bed she was very short of breath and had to sleep propped up on pillows. The next day she remained in bed, suffering off and on from pain in the interscapular area, and always very short of breath. These symptoms had continued and ten days later she entered the hospital. The pain in the interscapular area had persisted and the shortness of breath had increased. She spoke of having "spells" two or three times a day, consisting of an aggravation of the pain with more severe dyspnea than she had during the intervals. She had lost her appetite. She stated that during the previous two years she had fallen off about twenty-five pounds in weight.

*Examination.* Temperature 99.4°; pulse 84; respirations 56; blood pressure, systolic 145, diastolic 105.

The patient was a well-developed and fairly well-nourished colored woman who evidently had lost a good deal of weight. She was propped up in bed with extreme dyspnea. The breathing was rapid and shallow, panting in character. There was no cough. The mucous membranes were a little pale and there was a moderate degree of cyanosis. The eyes were normally prominent, pupils equal, regular, reacted actively. Extraocular movements were well performed. The fundi showed moderate arterial changes, otherwise they were normal. The teeth were in very bad condition, there was marked caries and pyorrhea. The tongue was heavily coated. The throat showed no noteworthy abnormality. There was no enlargement of the superficial lymph nodes. The thyroid was not enlarged. The chest was well formed and symmetrical, movements equal on the two sides. The lungs seemed to be clear except for a few fine rales at the bases on deep inspiration.

The apex beat of the heart was in the fifth interspace 9 cm. from the midline. The heart was little if any enlarged, the area of dulness measuring 4 cm. to the right and 10 cm. to the left of the midline. The heart sounds were clear. There was a well-marked presystolic gallop. No dulness over the manubrium. The pulse was regular, equal at the two wrists; the vessel walls were moderately thickened. The abdominal wall was soft and relaxed. No tenderness, no masses. The liver and spleen not enlarged. The pelvic examination disclosed a profuse leukorrheal discharge, otherwise no important abnormality. The neurological examination was negative.

*Course in the hospital.* It is difficult to give a clear picture of the condition of the patient. At first she sat up in bed with very rapid, shallow breathing. Later she lay down with panting respiration. She was a picture of utter prostration. From time to time she had recurring episodes corresponding with what she spoke of as "spells". On these occasions the breathing became extraordinarily rapid, the pulse rate increased and she presented the picture of collapse. On admission the lungs were thought to be clear but a day or two later a patch of consolidation was noted in the left lower lobe at the angle of the scapula and from then on she dedeveloped slowly the signs of patchy consolidation of the lungs. At first the left side was involved and then the right, the process apparently always being more marked on the left. The roentgenogram showed extensive areas of consolidation throughout the lungs. At first very few rales were heard, later on they became somewhat more numerous. When she entered the hospital there was very little expectoration. This gradually increased in amount and later she had from half an ounce to an ounce of mucopurulent expectoration during the twenty-four hours. On admission the leukocyte count was at a normal or subnormal level, later it increased somewhat, finally going as high as 17,000. The sputum was carefully examined daily and twelve days after admission tubercle bacilli were discovered. This finding was confirmed by subsequent examinations. The condition of the heart changed but little. There were no murmurs and the heart was little, if any, enlarged. The extreme dyspnea continued, the respirations at times going to 60 to the minute. The pulse became more and more rapid, beating at the rate of 140 or more to the minute. From the time of her admission cyanosis steadily increased. During the latter part of her illness the patient was kept in the oxygen tent. She lost weight and strength and died of exhaustion twenty days after entering the hospital, thirty-one days after the acute onset of her illness.

*Laboratory examinations:*

Blood count: 10/6/33. Hgb. 80%; red blood cells 4,930,000; white blood cells 8,650; polymorphonuclear neutrophiles 78%. Eosinophiles 1–2%. The leukocyte count gradually rose finally reaching the high point of 17,800.

Wassermann Reaction on the blood serum was negative.

Sputum Cultures: Pneumococcus type IV and streptococcus.

Urine Cultures: No growth.

Agglutination tests: Tularemia—no agglutination.

Sputum: Mucopurulent. Numerous tubercle bacilli found on October 18 and again on October 23.

Urine: Specific gravity varied from 1.018 to 1.034; there was a trace of albumin. An occasional cast and a small number of leukocytes in the sediment.

Roentgenograms:

10/7/33. Tele.: M.R. 3.1; M.L. 9.8; A. 4.7; T. 25.1.
Chest: Extensive fibroid infiltration of the lungs probably due to an old tuberculosis.

10/18/33. Chest: Soft infiltration both lung fields, probably due to disseminated tuberculosis.

Electrocardiogram: 10/6/33. Normal sinus rhythm. Two auricular extrasystoles fall in the refractory period but do not give rise to ventricular responses. T waves upright in leads I and II, inverted in lead III.

The temperature varied from 99° to 103.6°.

The pulse rate varied from 80 to 140.

Respiratory rate varied from 30 to 64.

Again in this patient the date of onset of the illness is uncertain. It seems likely that it began before the day upon which severe pain came on in the interscapular area although she had worked hard in the fields up to that time. However this may be, great dyspnea must have come on almost at the very beginning of the illness because from the moment she took to bed shortness of breath was the outstanding symptom. The history of intense dyspnea coming on so quickly after stabbing pain in the interscapular area and without preceding cough or fever suggested heart failure rather than pulmonary disease. However, observation of the patient at once demonstrated that the extreme shortness of breath was pulmonary in origin, not cardiac. She was as comfortable lying down as propped up in bed. Her respiration was very rapid and shallow; it cannot be better described than to call it panting. She was a picture of utter prostration and exhaustion. Now and again there were periods when the breathing became extraordinarily rapid, as frequent as sixty to the minute, and at these times the pulse rate rose, the blood pressure fell and alarming symptoms of collapse came on. In contrast to the very great dyspnea the physical signs of pulmonary infiltration were surprisingly meagre. At the time of admission to the hospital, even though shortness of breath was then very pronounced, the medical house officer described the lungs as

being clear except for a few râles at the bases. Later the signs of spreading bronchopneumonia appeared but still they were always disproportionate to the extreme dyspnea. Then, too, the fever was low and the symptoms of intoxication not at all pronounced. In a word dyspnea and ever increasing cyanosis were the consp cuous symptoms.

It is apparent how very alike the symptoms were to those of the patient described as Case 2. The similarity was so close indeed that the house officers and visiting physicians were confidently predicting that the anatomical diagnosis would be the same in both, when their growing assurance was rudely shaken by the report that numerous tubercle bacilli had appeared n the sputum. Perhaps even then they should have defended their views more stubbornly, but it seemed mpossible to refuse to surrender them after having received this damaging report. The autopsy will demonstrate clearly that the first impressions were correct, and will explain how the unexpected intrusion of tubercle bacilli, which overthrew these impressions, came about.

In this case (Autopsy No. 13367), again, the *lungs* were diffusely involved in a process of fibrosis. There were fibrous adhesions covering the left lung. The pleura of the right lung was smooth. Throughout all lobes of both lungs there was a net-work of very fine, translucent gray lines, and there were firm gray and red areas. Focal areas of emphysema were widespread (Fig. 9). In addition to this diffuse alteration, there was, in the central part of the left upper lobe, a cavity 2 cm. in diameter. This had a caseous lining and a gelatinous content. In the same lobe there were scattered, caseous foci, 1 to 4 mm. in diameter, some encapsulated. Several similar foci were in the lower lobe. No tuberculous lesions were present in the right lung.

Microscopically, the pulmonary lesions in this case were like those in Case 2, except that here there was a greater amount of organization of intra-alveolar exudate, and the fibrous tissue was, for he most part, older than that in Case 2 (Fig. 10). In some places, however, the earlier stages of the process were present, and fibroblastic proliferation was still in progress. Eosinophils were numerous. There was very little intimal thickening in the pulmonary vessels. The changes in the bronchioles were identical with those in Case 2.

The fact that the lesions in this case were, for the greater part, older than most of those in Case 2, although the duration of symptoms was supposedly about 2 weeks shorter, may be due to the recorded unreliability of the history in Case 2, or to the possibility that the actual onset of the disease may not be accompanied by symptoms severe enough to attract marked attention.

The tuberculous lesions in the left lung were characteristic. Tubercle bacilli were stained in numbers in the sections. These localized tuberculous lesions in the left lung were altogether unrelated to the diffuse fibrosis thoughout both lungs. No stainable bacteria were present in the latter lesions, except for occasional foci that contained a few large, Gram positive bacilli. Post-mortem culture of the lungs yielded a gamma streptococcus and an unidentified spore-forming bacillus. These bacteria were probably the result of terminal aspiration.

The *heart* in this case had a normal epicardium, and a greatly dilated right ventricle, which was also hypertrophied. The left ventricle was on the small side of normal, measuring only 1 cm. in thickness. It was not dilated. The coronary vessels were normal. The myocardium was normal microscopically and macroscopically.

The *aorta* was normal.

The only other pertinent findings were subcutaneous edema, no excess of fluid in the serous cavities, and visceral chronic passive congestion.

## CASE 4

Unit History No. 285,117. A white woman, 68 years of age, was admitted to hospital on the service of Dr. Charles R. Austrian, February 16, 1943 complaining of shortness of breath, cough and general malaise. She always had been a healthy woman except for a history of thyroid disturbance. At 19 years of age she had developed nervousness, palpitation, loss of weight and prominence of the eyes. A diagnosis of hyperthyroidism had been made and without treatment all of these symptoms had subsided. In 1935 she had had a return of great nervousness and the basal metabolic rate at that time had been plus 28. She had taken Lugol's solution for a year with gradual improvement. The basal rate in November was −11.

Four months before admission to the hospital the patient had begun to feel generally badly, developed a cough and had shortness of breath on exertion. The physician whom she consulted ascribed her symptoms to mild heart failure and advised rest and digitalis. After this treatment she had not improved, her symptoms slowly but steadily growing worse. January 19, 1943 she had entered a sanatorium and remained there for eleven days but during this period of rest she did not improve. Her cough became worse and she raised small amounts of yellowish mucoid material. There had been no shortness of breath while at rest and no peripheral edema.

*Examination:*

T. 98.8°; P. 78; R. 22; B/P 115/65.

The patient was a well developed, somewhat undernourished woman in no acute distress. She was pale and looked rather worn. There was a little shortness of breath and slight cyanosis. The eyes were normally prominent and reacted actively. The extraocular movements were normal. The fundi were normal except for slight arteriosclerotic changes. Most of the teeth had been extracted.

The gums were in good condition. The tongue was normal in appearance. The pharynx showed nothing remarkable. There was no enlargement of the superficial lymph nodes. The thyroid was not enlarged. The chest was rather long and thin, symmetrical, and respiratory movements, though limited, were equal on the two sides. The patient coughed frequently and any attempt at deep breathing brought on severe paroxysms of coughing. The percussion note was impaired over both lungs from the angle of the scapula to the base, the impairment being more pronounced on the right side. Breath sounds were blowing in quality, in places tubular, and numerous fine crepitant rales were heard over both lower lobes, also a few sonorous rales. In the right axilla there was a questionable friction rub. The heart seemed not to be enlarged, the sounds were clear and of normal quality except for a soft blowing systolic murmur at the apex. The second aortic sound was somewhat accentuated. The pulse was slow and regular, the peripheral vessels only moderately thickened. The breasts showed nothing abnormal. The abdomen was normal in appearance, the wall soft and relaxed; no tenderness; no masses were felt. The edge of the liver was just felt at the costal margin on deep inspiration. The spleen was not enlarged. The neurological examination was negative.

*Course in hospital.* The patient was in the hospital fifty-nine days. During the first three weeks the temperature was only a little elevated, varying from 97.6° to 100°. On March 13, following a chill, the temperature rose to 104.4° and during the following two weeks varied from 99.4° to 103°, gradually falling to lower levels. From March 27 to April 2 the temperature varied from 98.6° to 100°. On March 3 it rose suddenly to 103°, then gradually fell and at the end of four days had reached 99°. It then varied from 97° to 100° until April 13 when it rose to 102.6° and during the final two days of illness varied from 100.6° to 102.4°. The pulse rate at first varied proportionately to the fever but during the last two weeks of life it remained high, irrespective of the temperature variations. From the time of admission to hospital the patient coughed a great deal but raised little or no expectoration. On March 14, following a chill with rise of fever, the signs over the lungs indicated a rapid advance of the process in the lower lobes. The evidences of consolidation were more pronounced and moist rales were heard over the upper lobes as well as over the lower. Respirations became shallow, rapid and labored. The patient was prostrated and from time to time there was delirium. On March 23 the physical examination indicated the presence of fluid at the base of the right lung. Thoracentesis yielded 15 cc. of straw-colored fluid containing 900 cells per cu. mm. 60% of which were red blood corpuscles; 40% leucocytes; 90% of the leucocytes were mononuclears, 10% polymorphonuclears. Cultures from the fluid remained sterile. Following thoracentesis a loud friction rub was heard over the right side. On March 27 there was a pronounced swelling of the left side of the neck, thought to be due to swelling of the submaxillary salivary gland. At this time the patient was semicomatose and in a critical condition. A few days later she was better, more alert, not nearly so deeply intoxicated, and for a few days her

condition was improved. On April 2 she had a shaking chill and the temperature rose to 103.2°. Following this the shortness of breath became more pronounced. It had been difficult to feed the patient and from time to time there had been vomiting. On April 3rd the right leg was found to be swollen due, it was thought, to thrombophlebitis of the right femoral vein. There was difficulty with urination, the bladder often was distended, and catheterization was necessary. Evidence of fluid in the right pleural cavity persisted and signs of consolidation over the left lower lobe had become more pronounced. On April 13 the right pleural cavity was tapped again and 300 cc. of turbid light yellow fluid was obtained having a specific gravity of 1.015. Cultures of the pleural fluid remained sterile and no tubercle bacilli were found in smears. From them on the patient rapidly grew worse, she became weaker, more deeply prostrated, the pulse rapid, and on the afternoon of April 15th she died.

*Laboratory examinations:*

*Blood count:* Feb. 17th. Hbg. 13.5 gms. RBC 4,570,000 WBC 15,000 with 88% PMN cells. The leucocyte count at first varied from 10,000 to 18,000. March 27th it rose to 35,000; on March 29th to 50,000; on April 3rd to 55,000. The count then fell and on April 5th was 12,000. Eosinophils, 2–5%.

S.T.S. Negative.

Urine: Spec. Gr. varied from 1.014 to 1.018. It contained from a trace to 2 plus albumin. At first there were a few leucocytes in the sediment, toward the end many leucocytes with an occasional hyaline and granular cast.

Phthalein test of kidney function yielded an excretion of 55% in two hours.

Urine cultures: At first sterile, later a heavy growth of Alpha streptococcus fecalis.

*Electrocardiogram:* Feb. 17th. Normal sinus rhythm. T-I and II upright; T-III diphasic, T-IVF upright. Q-III wave of borderline significance. Otherwise the record is normal.

*Roentgenograms:*

Feb. 17th. Chest: There is an extensive non-tuberculous chronic process in lower lobe of each lung, more particularly on right side. Slight changes seen in the aorta. The heart is obscured so that a fair estimation of its size cannot be obtained.

Mch. 6th. No change from previous examination.

Mch. 18th. Portable examination of the chest shows infiltration involving the entire right lung and a major portion of the left lung. There has been a definite advance in the process since March 6th.

Apr. 6th. There is evidence of clearing of the pneumonic process in each lung.

This is an unusual clinical picture of a sub-acute pulmonary infection. With the manifestations of advancing consolidation of the lungs,

the patient had harassing cough, though no sputum, and a degree of shortness of breath seldom seen in any of the usual forms of pulmonary inflammation. The patient entered the hospital after she had been ill four months; unfortunately, therefore, we do not know the details of what may have occurred during this period. Nevertheless, the fact that at first physicians interpreted her symptoms as indicating heart failure permits us to surmise that at that time the evidence of disease of the lungs must have been inconspicuous and the shortness of breath quite out of proportion to whatever abnormality may have been found in the lungs. Even from only the scanty history of these early weeks we may conclude that at that stage the illness bore no resemblance to the usual forms of lobar or lobular pneumonia. Upon the wards of the hospital, no diagnosis was proposed that seemed satisfactorily to explain the clinical course of this remarkable illness. Tuberculosis was at once suggested, yet certainly this was not the picture of advancing tuberculosis. Nevertheless, in patients over sixty, childhood forms of tuberculosis sometimes occur, which run a course quite different from that of the usual forms of adult tuberculosis. Organization of a pneumonic consolidation was proposed but the available evidence was against the patient having had pneumonia and, moreover, it was obvious that the disease in the lungs was steadily advancing. Bronchial carcinoma with bronchial obstruction and secondary infection of atalectatic lobes and also actinomycosis were considered but there was nothing whatsoever to support either of these diagnoses. At the end the presumptive diagnosis was some form of organizing pneumonia or tuberculosis.

At autopsy (No. 18330) the surfaces of the *lungs* were roughened by fibrin, and there were a number of adhesions between the visceral and parietal pleurae. There was a thrombus in a branch of the right pulmonary artery, doubtless an embolus from the veins of the right leg, which was enlarged on measurement, though no thrombus was found in the femoral vein as far as it was explored. On section, the cut surfaces of the lungs were edematous, and there were rather translucent, firm, gray areas scattered throughout all lobes of both lungs. There were suggestive but not altogether definite macroscopic scars. The hilar lymph nodes were not enlarged.

Microscopically, there was a marked post-mortem growth of colonies of aspirated bacteria throughout the sections, with no associated inflammatory reaction, and the tissue was in a poor state of preservation. All of the sections from all lobes

showed a diffuse thickening of the alveolar walls, and there were also small scars which had obliterated the architecture entirely. It was clear that, in places, organization of intra-alveolar exudate had occurred. The thickened alveolar walls were edematous, and contained wandering cells, fibroblasts, collagen fibers and newly formed capillaries. The lining alveolar cells were greatly enlarged, and hyaline membranes were plentiful. Many alveoli contained coagulated protein, and there were occasional mononuclear cells and much desquamated alveolar epithelium within them (Fig. 8). Here and there they contained hemorrhage which, in places was undergoing organization. The bronchiolar epithelium was in places low and flattened, or squamous, and in places low cuboidal epithelium had proliferated from the bronchioles to line adjacent air sacs. Some of the pulmonary arteries showed slight intimal thickening. In this case eosinophils were only occasionally encountered.

The *heart* weighed 345 gms. There were several fibrous adhesions binding the visceral and parietal pericardial surfaces. Aside from slight dilatation of the left auricle none of the chambers were abnormal in size or thickness of their walls. The mitral valve was thickened and the cusps slightly fused at one point. The aortic valve was slightly thickened. There was moderate sclerosis of the coronary arteries. The myocardium contained a few microscopic scars, which were irregularly distributed, with no especial relation to blood vessels or septa that might suggest an old rheumatic process.

The *aorta* was sclerotic, with no evidence of syphilis.

The only other pertinent findings were 300 cc. of fluid in the right thoracic cavity, and 260 cc. in the left; and fresh central necrosis of the liver, possibly related to the anoxaemia, for there was no visceral chronic passive congestion.

## DISCUSSION

The pathological peculiarities of this condition are, therefore, (1) the type of inflammation (edema, hemorrhage, few leucocytes) which differs from that of ordinary pneumonia produced by pyogenic bacteria; (2) the enlargement of the lining alveolar epithelial cells; (3) the necrosis of alveolar and bronchiolar epithelium; (4) the formation of a hyaline membrane that lines the alveoli; (5) the marked edema and fibrin deposit in the alveolar walls; (6) the extensive, diffuse and progressive interstitial proliferation of fibrous tissue throughout all lobes of both lungs, associated with focal organization of intra-alveolar hemorrhage; (7) the presence of eosinophils in the interstitial tissue in three of the four cases; and (8) the absence of stainable bacteria in the lesions.

The poor state of preservation of the lungs in this case rendered

an accurate study impossible, but the condition characteristic of the preceding cases seemed to be present in a reasonably persuasive form.

From the pathological anatomy and the symptoms of these four patients, we may reconstruct the clinical picture of an uncommon and remarkable disease. Pulmonary inflammation of the peculiar type described above develops insidiously with little local or constitutional disturbance. There are none of the symptoms which usually mark the advent of bronchopneumonia; there is little fever, the patients are not incapacitated or forced to bed, the leucocytes are little if any increased. Very shortly after the onset, connective tissue begins to proliferate within the alveolar walls, and soon dyspnea comes on and grows increasingly severe as a result of the disturbance of the relation of the capillaries to the alveolar lumen by the interstitial growth of fibrous tissue, and the gradual compression of alveolar spaces by the rapidly advancing fibrosis. Two of our patients died of slowly progressing suffocation. What may happen if this stage of the disease is outlived is illustrated by the patient described as Case I. As pulmonary fibrosis increases and spreads, the circulation in the lungs is impeded, the pressure in the pulmonary artery is increased, and soon the right ventricle becomes dilated and hypertrophied. In three of the four cases, the right ventricle was appreciably enlarged and its walls thickened, although in Case 2 only forty-six days had elapsed from the onset of symptoms to the time of death and in Case 3 only thirty-one days. As the pressure in the pulmonary circulation steadily rises a constantly increasing burden of work is thrown upon the right side of the heart. Soon or late the symptoms of congestive heart failure appear and steadily advance until finally death occurs from myocardial insufficiency. We do not mean to imply that when the disease once sets in, death necessarily must always follow. Postmortem observations lead us to believe that localized forms of the disease may occur from which patients recover, for we have occasionally seen in the lungs of patients dying of other causes small or larger areas of a web-like pulmonary fibrosis similar in appearance with the late stages of this disease. About the cause of the disease there is nothing certain to say. The fact that studies of the sputum fail to show the presence of a predominating organism, and that at autopsy no bacteria can be stained in the lesions, suggests that perhaps it may be an

invisible virus. The possibility of a chemical irritant has, however, to be considered.

In a search of medical literature we have been unable to find a systematic description of the disease. However, here and there we have come across reports of cases with clinical history and post-mortem findings much like those of our patients. For instance, Doenecke and Belt (1) (2), under the title "Fatal Fibrosis of the Lungs Resulting from Industrial Exposure to Radium," describe the illness of a young chemist 35 years of age. For two years he had worked in the laboratory with preparations of radium and mesothorium under conditions which warranted the supposition that he had been exposed to large doses of emanations. At the end of that period, shortness of breath had begun, and had grown steadily worse until he died of suffocation two and a half years later. The description of the gross and microscopical appearance of the lungs coincides with what was present in our cases. There was intense diffuse fibrosis of the lungs restricted to the interstitial tissues.

Kneeland and Smetana (3) report a group of cases of bronchopneumonia of unusual character and undetermined etiology. Their Case 9 corresponds clinically and anatomically with our cases. A white woman 47 years of age entered hospital after six weeks of illness characterized by fever, cough and blood-streaked expectoration. There had been a brief period of improvement followed by relapse. On admission to the hospital she was very ill and deeply cyanotic. Over the lungs were the signs of an extensive bilateral bronchopneumonia. Cyanosis and dyspnea were conspicuous and the patient was kept constantly in an oxygen tent. She developed cor pulmonale with symptoms of congestive heart failure. She died ten weeks after the onset of symptoms of extreme pulmonary insufficiency. The description of the lungs and the reproduced photomicrographs lead us to conclude that this was an instance of the disease we are describing. In this case, in addition to the pulmonary fibrosis, there were lesions in the pulmonary arteries characteristic of periarteritis nodosa. Rich (4) (5) and Rich and Gregory (6) have since shown that vascular lesions of this type can result from anaphylactic hypersensitivity, and that they can result from hypersensitivity to the sulfonamides. Since the patient of Kneeland and Smetana had received sulfonamide ther-

apy, the periarteritis nodosa was probably referable to that, and independent of the pulmonary fibrosis. None of our patients with pulmonary fibrosis had vascular lesions of that type.

SUMMARY

This report describes a clin cal and pathological entity characterized by a peculiar, progressive, diffuse fibrosis of the pulmonary alveolar walls, leading to deficient aeration of the blood with resulting dyspnoea and cyanosis, and to enlargement and eventual failure of the right side of the heart. The etiology of the condition is at present undetermined.

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## ILLUSTRATIONS

## EXPLANATION OF ILLUSTRATIONS

(Photographs by Mr. Milton Kougl)

FIG. 1. Lung of Case 2. There were diffuse, firm areas caused by thickening of the alveolar walls and fluid and hemorrhage in the alveoli, but no macroscopic scars.

FIG. 2. Alveolar wall of Case 2, thickened by edema, fibrin, wandering cells and beginning proliferation of fibroblasts. The capillaries are dilated. Note hyaline membrane above and enlarged lining alveolar epithelial cells on lower surface.

FIG. 3. Alveolar wall of Case 2, thickened by edema, fibrin, wandering cells and beginning proliferation of fibroblasts. Capillaries are dilated. Hyaline membrane above. The alveolar lining cells are enlarged and some have been destroyed.

FIG. 4. Part of greatly thickened alveolar wall of Case 2. Note new formation of capillaries, proliferating fibroblasts, and infiltrating mononuclear cells.

FIGS. 5 AND 6. Lower magnification showing greatly thickened alveolar walls of Case 2. Note hyaline membranes.

FIG. 7. Area in lung of Case 2, showing more advanced fibrosis of alveolar walls.

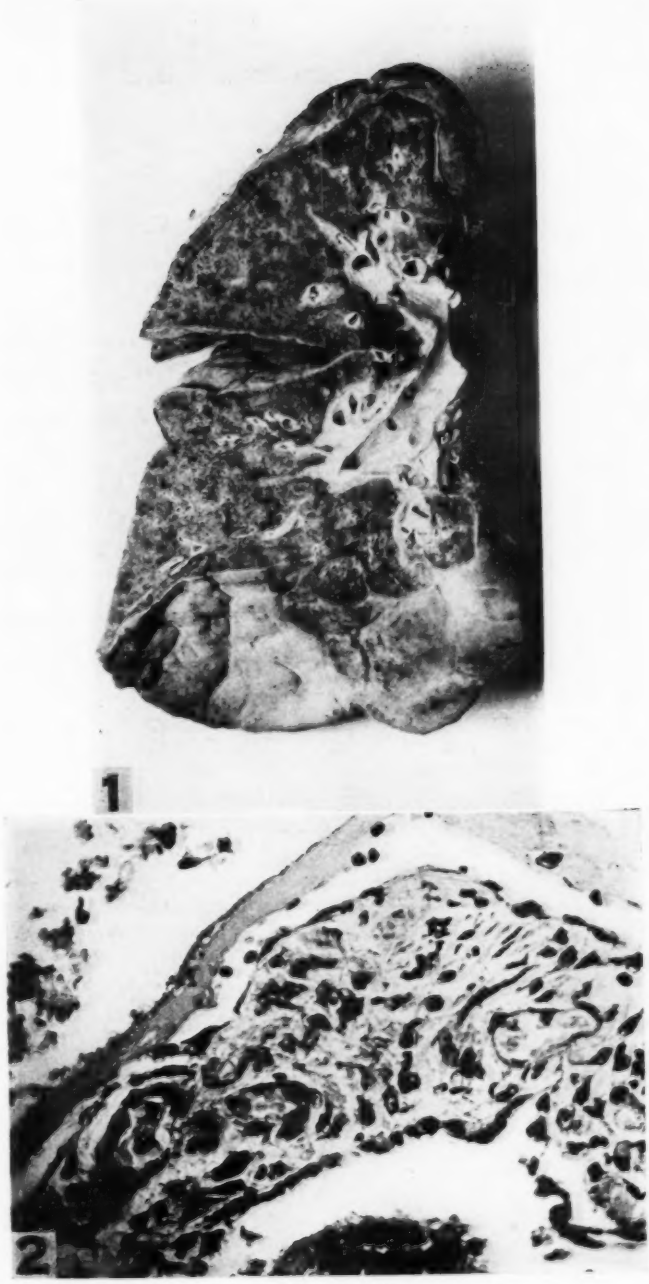
FIG. 8. Oedema and early fibrosis of alveolar walls in Case 4. Note hyaline membranes.

FIG. 9. Lung of Case 3. The scarring is too fine to be seen in the photograph. Focal emphysema associated with the fine scarring can be seen, particularly in the upper part of the upper lobe.

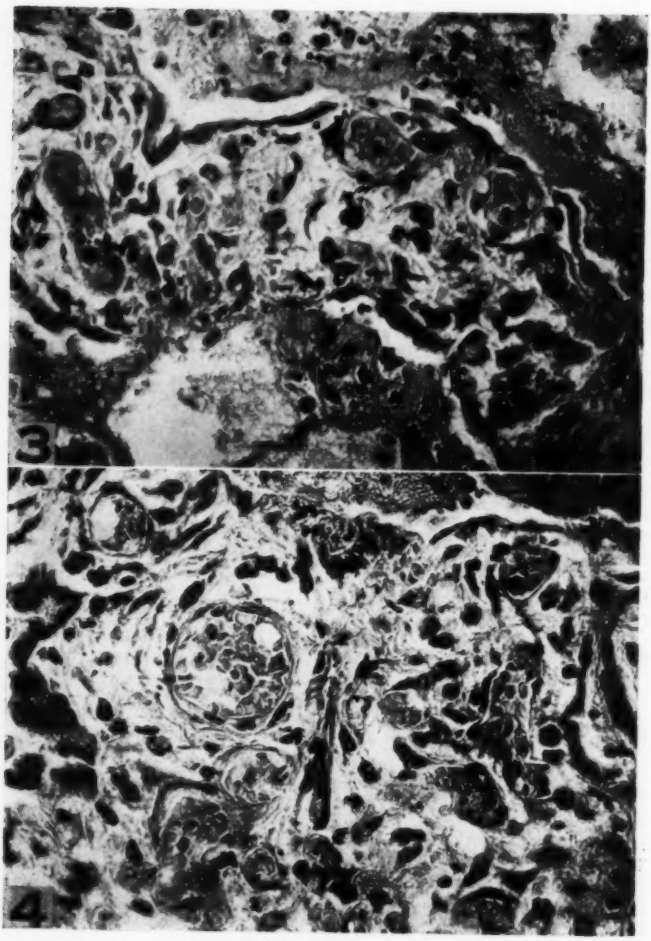
FIG. 10. Fibrosis of alveolar walls in Case 3.

FIG. 11. Lungs of Case 1. The diffuse fine scarring is too inconspicuous to be seen in the photograph. Foci of emphysema associated with the scarring can, however, be seen.

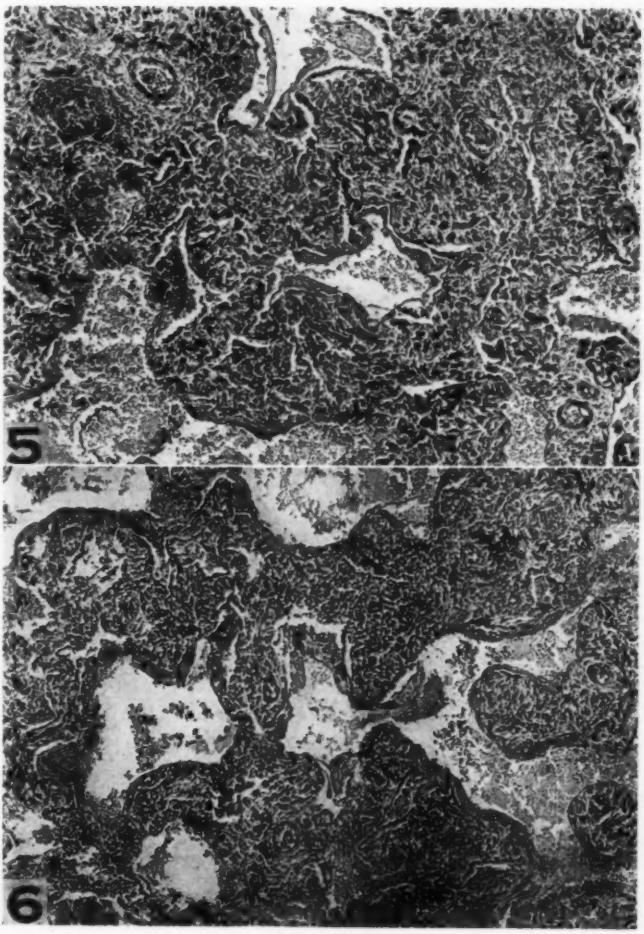
FIG. 12. Fibrosis of the alveolar walls in Case 1.



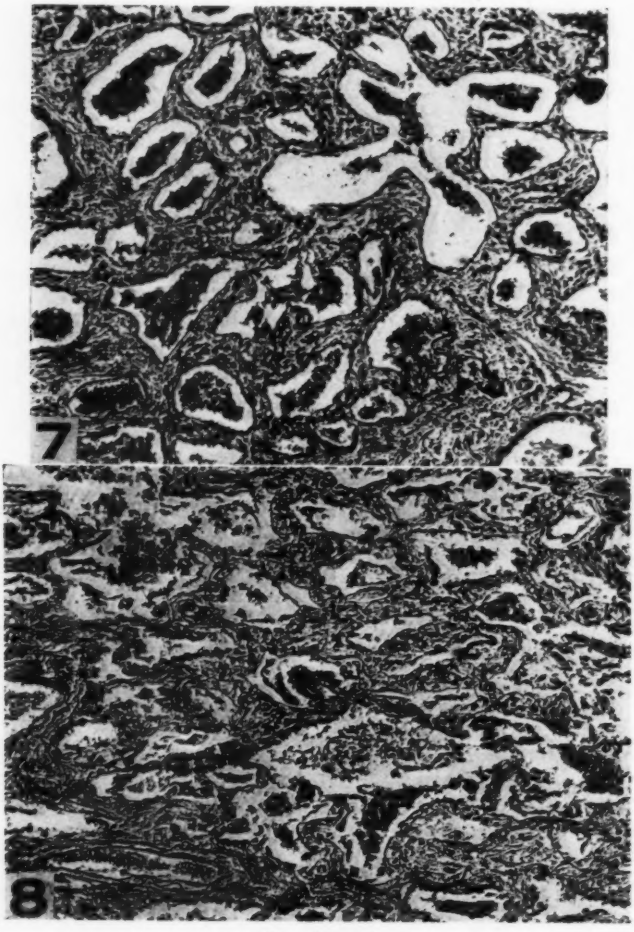
FIGS. 1 AND 2



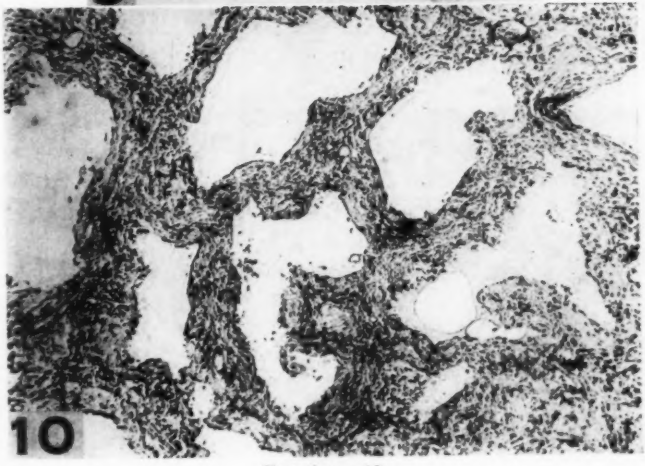

FIGS. 3 AND 4



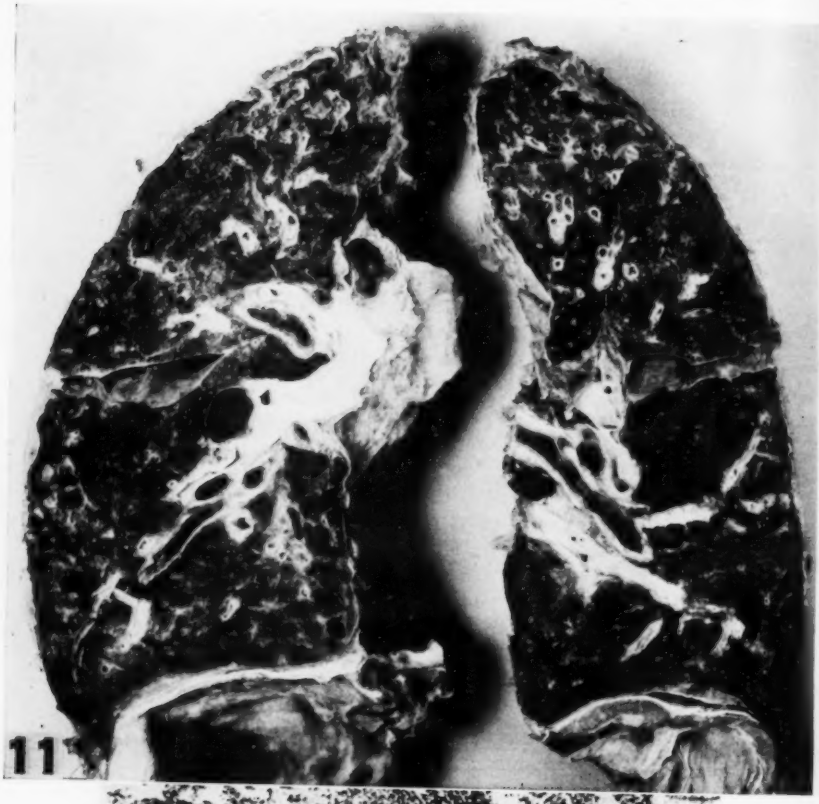

FIGS. 5 AND 6

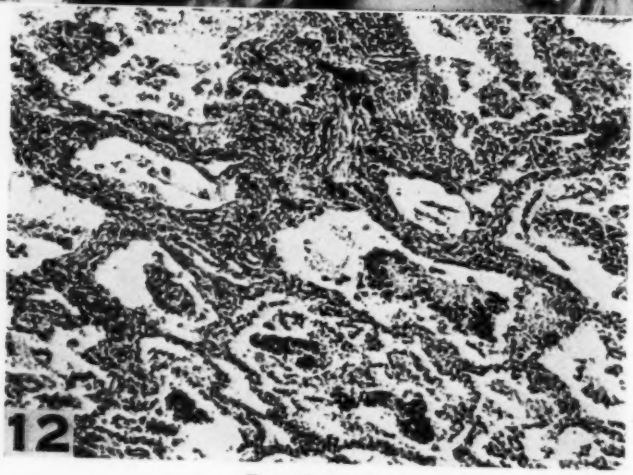



FIGS. 7 AND 8




FIGS. 9 AND 10




FIGS. 11 AND 12

# GRANULOMA INGUINALE AS A CAUSE OF ARTHRITIS AND OSTEOMYELITIS

## Report of a Case

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That lesions of granuloma inguinale occur in parts of the body other than the genitalia is well established. It is believed generally that such lesions result from direct contact with or direct spread from an active local lesion, although it has been suggested that the disease is a generalized infection. In the reports of the extragenital and extrainguinal lesions arthritis and osteomyelitis have been mentioned only rarely, and the evidence is certainly inconclusive that these were manifestations of granuloma inguinale.

Polyarticular arthritis or osteomyelitis proved to be due to granuloma inguinale occurred in several patients under our care. The detailed studies of one of these cases are recorded because it is felt that the findings are of value as demonstrating that granuloma inguinale may have a systemic dissemination, and that in this case clinical "rheumatoid arthritis" was caused by a specific infecting agent recovered from the joint tissues.

### CASE HISTORY

R. W. (# 299347), a twenty-year old, colored female was first seen in the Johns Hopkins Hospital August 11, 1943 complaining of a genital sore and abdominal pain. Eleven weeks before, the patient had had her last sexual exposure with a companion on whom she had noticed a red penile sore. Four weeks later the patient developed a small vulvar ulcer which grew progressively worse, and was associated with a watery vaginal discharge and tender swelling in both groins. There were also episodes of low abdominal pain which increased in severity. During these seven weeks the patient received oral sulfonamides at the direction of her local physician, and had no relief. She had persistent fever, and lost fifteen pounds in weight.

The physical examination on admission to the Johns Hopkins Hospital revealed a thin, under-nourished colored girl who appeared chronically ill. The temperature was 101.4°, pulse 128, respirations 20, and blood pressure 115/70. In the left lower quadrant of the abdomen extending toward the flank there was palpable a large, firm, tender mass which on bimanual pelvic examination was found to be continuous with tender induration extending across the bases of both broad ligaments and the cul-de-sac of Douglas. There were several small, soft, tender subcutaneous nodules in both groins. Edema was present in both labia majora and the left labia minora. At the vaginal fourchette there was a granulating ulcer extending about three centimeters into the vagina and toward the right labia minora. There was a profuse, thick, whitish discharge from the vagina, but the cervix appeared healthy.

On August 14 a biopsy of the lesion at the vaginal fourchette was performed. Study of this tissue showed Donovan bodies in large macrophages and masses of plasma cells in the tissues. Sitz baths and vaginal douches gave no relief. Ten days later (August 24) the patient developed migratory pains in both knees, both elbows, and the left foot, followed in four days by a fusiform swelling of the left third toe. On September 1 a radical vulvectomy was performed, and early granulating ulcers on the cervix and right lateral vaginal wall were fulgurated. Microscopic examination of the tissue from the vulva again revealed Donovan bodies in scattered macrophages together with many plasma cells in the exudate.

Pain and swelling persisted in the elbows, knees, wrists, and toe. On the fifteenth postoperative day the swelling in the left knee increased markedly; and simultaneously there developed over the frontal bones two tender, soft nodules which never receded. Aspiration of the left knee produced hazy, straw-colored fluid which was sterile in cultures for acid-fast bacilli, *N. gonorrhoea* and other pyogenic organisms. A short course of diathermy treatments to the pelvis caused an exacerbation of the joint symptoms.

On November 4 (four months after the appearance of the original genital sore) because of the persistent ulcer the left third toe was amputated by a guillotine procedure. Microscopic examination

revealed osteomyelitis of the proximal phalanx and chronic inflammation of the subcutaneous tissues. In both the bone and soft tissues there were many plasma cells and scattered large macrophages filled with Donovan bodies. The joint manifestations subsided gradually, and the joints assumed the characteristic appearance of a "rheumatoid arthritis". November 22 the right elbow was explored, and the synovium was found to be thickened and friable as in any chronic non-specific arthritis, while the articular cartilages appeared clean and smooth. Microscopic sections of the tissue removed at operation showed granulation tissue in which plasma cells predominated, and large macrophages filled with Donovan bodies were present in smaller numbers, as in all the other lesions. The operative incision healed per primum, and remained healed.

Throughout the hospital course of four months the patient had an irregular spiking temperature of 98° to 103°. She received oral sulfadiazine 3–6 grams daily for seven weeks without apparent effect on the lesions or the fever. Four injections of Fuadin had no effect on the lesions, and were associated with nausea, headaches, and fever. The hemoglobin level ranged from 33 per cent to 60 per cent despite frequent transfusions of whole blood. The white blood cell count varied from 13,000 to 27,000.

Masses of macrophages containing Donovan bodies grew in tissue cultures of material from the soft tissue and bone of the left third toe, and from the tissue removed from the right elbow joint. Cultures on all ordinary media of fluid and tissue from the right elbow were sterile.

The patient left the hospital after four months, symptomatically improved and with no stiffness or limitation of motion of any of the joints. Subsequently there was a gradual exacerbation of the joint manifestations, and two months later (six months after the initial onset) the wrists, knees, and ankles were swollen, hot, and tender. The interphalangeal joints of all the fingers showed fusiform, tender swellings with the same type of draining granulating ulcers over the joints of the left fourth and fifth fingers as occurred originally on the left third toe. The site of amputation of the toe appeared clean and almost healed. The genital lesions had recurred, but the operative incision of the right elbow remained healed.

LABORATORY FINDINGS

| | |
|---|---|
| Blood serologic tests for syphilis. | Repeatedly negative. |
| Frei skin test. | Repeatedly negative. |
| Ito skin test. | Repeatedly negative. |
| Lymphopathea venereum complement fixation test on blood serum. | Negative. |
| Gonorrhea complement fixation test on blood serum. | Anticomplimentary on 9–18–43 and 11–9–43. Negative on 9–29–43. |
| Blood serum agglutinations for Typhoid "O", Dysentery, and Brucella. | Negative in all dilutions. |
| Blood serum agglutinations for Typhoid "H". | Positive in 1:20, 1:40, and 1:80 dilutions only. |
| Blood serum agglutinations for Paratyphoid B. | Positive in 1:20 and 1:40 dilutions only. |
| Blood cultures. | Sterile. |
| Urine cultures. | Sterile. |
| Cultures of fluid from left knee joint. | Sterile for acid-fast bacilli, *N. gonorrhea* and other pyogenic organisms. |
| Cultures from ulcer on left third toe. | Sterile for *N. gonorrhea* and other pyogenic organisms, and fungi on 9–29–43. Heavy growth of Diphtheroids and *Staph. albus* on 10–19–43. |
| Blood non-protein nitrogen. | 23 mgm. per cent. |
| Fasting blood sugar. | 84 mgm. per cent. |
| Total serum proteins. | 10.69 grams per cent. |
| Serum albumin. | 2.94 grams per cent. |
| Serum globulin. | 7.75 grams per cent. |
| Blood uric acid. | 3.6 mgm. per cent. |
| Blood calcium. | 10.9 mgm. per cent. |
| Blood phosphorus. | 5.8 mgm. per cent. |
| Blood phosphatase activity. | 4.4 Bodansky units. |
| Blood sulfadiazine levels. | 1–14.2 mgm. per cent. Average 5–7 mgm. per cent. |
| P.S.P. kidney excretion test. | After 15 minutes: 15 per cent.<br>After 30 minutes: 35 per cent.<br>After 75 minutes: 15 per cent.<br>After 135 minutes: 10 per cent.<br>Total: 75 per cent. |
| Radiograms of the left knee. | Normal. |
| Radiograms of the left foot. | October 4: The proximal phalanx of the third toe shows a circumscribed area of decreased density. |
| Radiograms of the right elbow. | October 16: There are destructive changes seen localized in the olecranon process of the ulna, and calcium deposits appear in the adjacent soft tissues. |

| | |
|---|---|
| Radiograms of the bones of the skull. | October 16 and November 1: Normal. |
| Electrocardiogram. | No significant abnormalities. P–R interval 0.14. |
| White blood cell counts. | 13,000 to 27,000. |
| Differential white blood cell count. | Juvenile polymorphonuclear cells = 15 per cent. Adult polymorphonuclear neutrophilic cells = 85 per cent. |
| Hemoglobin. | 4.8–8.7 grams per 100 cc. blood (33–60 per cent). |
| Smears of fresh blood. | No sickling. |

SUMMARY

A case of granuloma inguinale of the genitalia with associated arthritis of the joints of the extremities, and osteomyelitis has been described. Microscopic sections of tissue from the bone, joint, and genital lesions showed Donovan bodies in large macrophages, together with massive collections of plasma cells in the exudate. Continuous tissue cultures were made of material from the lesions (arthritis and osteomyelitis), and in these cultures the organism grew for several weeks. Typical Donovan bodies were seen in the macrophages and in large mesenchyme cells, and were also seen in the medium between the tissue cells as small colonies not much larger than the cells. Cultures on ordinary media of material from the lesions were sterile.

Further studies of similar cases are being carried out, and it is expected that the results will be described in a subsequent report.

The authors are indebted to Dr. Sam S. Blackman, Jr., for the microscopic examinations, and to Dr. George O. Gey for the tissue culture studies.

# PROCEEDINGS OF THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

## Held in Hurd Hall, February 14, 1944, Dr. Alfred Blalock, Presiding

*1. Report of a Case of Perirenal Hemorrhage from Spontaneous Rupture of an Intrarenal Artery.* Dr. W. P. Longmire.


SUMMARY

This is a case report of a massive perirenal hemorrhage arising from the spontaneous rupture of an arteriosclerotic vessel in the parenchyma of the right kidney. A nephrectomy was performed, and the patient made an uneventful recovery.


One similar case has been reported,[1] but the actual site or condition of the ruptured vessel was not demonstrated. No similar case was found in over 18,000 autopsies performed at the Johns Hopkins Hospital; nor is there a comparable case in the files of the Brady Urological Institute.

C. H., a 66 year old male, was admitted complaining of "pain in the stomach". His past history was non-contributory. Twelve hours before admission the patient had a sudden dull aching pain throughout the right side of the abdomen. The pain persisted and there were cramplike exacerbations at irregular intervals. He felt nauseated and vomited once. He had a desire to defecate but his bowels did not move. His stools and urine had been normal. There was no history of trauma.

Physical Examination. Temperature 100.8°F. (rectal), pulse 86, respirations 20, blood pressure 172/126. The mucous membranes were slightly pale. There was marked generalized arteriosclerosis. Moderate abdominal distention and generalized tympany were noted. There was boardlike rigidity of the entire right side of the abdomen and right flank. Tenderness could be elicited in the right middle and lower abdominal regions with firm palpation.

The white cell count of the blood was 24,160, and the hemoglobin content was 10.0 gms. A specimen of urine could not be obtained.

The preoperative diagnosis was acute appendicitis with perforation.

At operation a large perirenal hematoma was found which arose from a rent in the inferior pole of the right kidney. A transperitoneal nephrectomy was performed. The postoperative course was uneventful.

Pathological diagnosis: (1) Chronic pyelitis. (2) Foci of chronic pyelonephritis. (3) Marked sclerosis of extrarenal and intrarenal arteries and arterioles. (4) Necrosis, inflammation and rupture with hemorrhage of solitary intrarenal artery.

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[1] Speese, J., Surg., Gynec. and Obst., **16**: 571, 1913.

DISCUSSION

*Dr. Hugh J. Jewett* pointed out that the sequence of events in this case was most peculiar and unorthodox for spontaneous rupture of a deeply lying cortical vessel. The extravasation of blood, instead of extending into the hilum or calyx and filling the kidney with blood, occurred outward. Even so, it should have been arrested by the capsule with the formation of a sub-capsular hematoma, instead of which rupture of the capsule occurred. A rupture of the capsule with massive intraperitoneal hemorrhage may occur in children who have relatively little perirenal fat, but in subjects over 10 years of age it is almost unheard of except in penetrating injuries. It seems probable that the actual cause of the hemorrhage was unrecognized trauma which split the capsule and tore open the parenchyma down to the diseased vessel.

Dr. Jewett further commented on the difficulties of diagnosis in these cases. Pyelography would have been of no value here. Careful clinical observations are of the greatest help, but in this instance an accurate preoperative diagnosis was impossible. Dr. Longmire was to be complimented for his handling of a serious emergency.

*Dr. Rich* stated that he had examined the material and that the cause of the hemorrhage was not clear. The condition did not appear to be periarteritis nodosa. A congenital aneurysm which may occur in the kidney as well as in the brain was a definite possibility.

*2. Sjögren's Syndrome.* DOCTOR A. L. MACLEAN.

SUMMARY

In 1933, Sjögren, a Swedish ophthalmologist described an unusual condition, seen more often in women at or near the menopause, and characterized by dryness of the eyes and mouth from deficient lacrimal and salivary secretion, and enlargement of the parotid glands from secondary ascending infection by way of Stenson's ducts. His name is given to the syndrome of Keratoconjunctivitis Sicca, Laryngopharyngitis Sicca and enlargement of the parotid glands. The symptoms come on gradually and it may be a period of years before the typical clinical picture is complete. Arthritis has been found in 60% of the cases reported. Dryness of the skin, cyanosis of the hands and feet and achlorhydria are frequently present.

The cause has not been clearly shown. By some it has been ascribed to an involvement of the sympathetic nervous system. That the endocrine system may play a role has long been suspected. Sjögren believes it to be due to infection. Others attribute it to Vitamin A deficiency.

An early complaint is absence of tears on laughing or crying. There is stinging and burning in the eyes, marked photophobia in the late stages and reduced visual acuity. The ocular lesions are quite unique. The corneal surface becomes rough and hazy, particularly in the lower exposed part. Filaments of degenerated epithelium and defects (staining areas) when dyes are used, are usually seen. The

conjunctiva is usually swollen and congested. A characteristic stringy mucoid discharge is always present in the lower cul-de-sac. The bacterial flora is seldom anything but normal. Deep perforating ulcers, dense corneal scars and iritis are rare complications. In the typical Sjögren syndrome the parotid glands, first one and then the other, become enlarged. Recessions occur in from three weeks to several months. Occasionally the swelling remains permanently. The mouth becomes dry and filled with a viscid secretion.

The microscopic pathology was carefully studied by Sjögren. The lacrimal and salivary glands all showed disintegration of the glandular structure, marked atrophy, some chronic inflammation with eosinophiles, and scarring. Sections of the eyes showed edema of the conjunctiva and desquamation of the corneal epithelium.

Deficient lacrimation can be determined by placing a strip of filter paper, 5 mm. wide and 30 mm. long, in the lower cul-de-sac and measuring the length of the moistened area in from one to five minutes.

The condition has to be differentiated from xerophthalmia due to A-avitaminosis, chronic conjunctivitis, mumps, calculus in Stenson's duct, tularemia, Parinaud's conjunctivitis, Boeck's sarcoid and Mikulicz's disease. General treatment is without effect. Local applications to the eyes are unsatisfactory. The best local treatment for the eyes is permanent and complete occlusion of the canaliculi.

In the last four years three typical cases have been seen at the Johns Hopkins Hospital.

DISCUSSION

*Dr. Alan Woods* expressed his gratitude to Dr. MacLean for calling attention to this syndrome. In the experience of the Wilmer Clinic the complete syndrome had not been encountered, but a number of cases of keratitis sicca had been seen, mostly in post-menopausal women. There was no question about the fact that the lacrimal glands were atrophied in this state, but the etiology of the condition was completely obscure. There was no evidence of vitamin deficiency or of a disorder of the sympathetic system, nor could trauma be implicated. The condition appeared to be just another menopausal complaint dependent on an endocrine disturbance that was not well understood.

*Dr. Halsey Barker* described studies which he had made upon the first patient, which had been referred to him by Dr. MacLean. Deficiencies of vitamins A and C had been carefully excluded. Because of the similarity of the glandular lesions to those observed in cystic fibrosis of the pancreas, studies of the pancreatic secretion had been made by Dr. Lay Martin; these showed all three pancreatic ferments to be present in normal amounts. Dr. Barker asked Dr. MacLean how patients with this condition would respond to tear gas, and whether they could peel onions with impunity.

*Dr. Arnold Rich* expressed his interest in this syndrome, and particularly in the possibility that it might have something to do with hypersensitivity. Such symptoms as arthritis and purpura were in accord with this thought, as was the presence

of an eosinophilic reaction about the ducts. Possibly the cystic dilatation about the ducts could be related to an increased viscous secretion which plugged the ducts as it did the bronchioles in asthma. The response of the lacrimal apparatus in hay fever was in keeping with this suggestion. He would like to ask Dr. MacLean if these cases had been studied from the point of view of hypersensitivity.

*Dr. L. Lee Hasenbush* expressed his interest in the lesions from the point of view of a tonomic imbalance. It seemed possible that the sphenopalatine, parotid, and otic ganglia were affected in this condition. The signs present including the dry skin might be due to an overflow of parasympathetic stimuli from the cranial nerve supply. Concerning the action of atropin and parasympathomimetic drugs, it was pointed out that after the salivary and mucous glands had already atrophied (perhaps as a result of parasympathetic overstimulation), response of those glands to such drugs would not be expected. He would also like to ask if the pulse showed any evidence of a vagal disorder.

*Dr. Blalock* asked about the differentiation of this condition from the Mikulicz syndrome, and whether prostigmin might be of value.

*Dr. MacLean* in closing stated that the condition could be sharply differentiated from the Mikulicz syndrome in which there was no disturbance in the flow of tears. Furthermore, in Sjögren's syndrome the lacrimal glands do not swell. Atropin had been used locally with a view to increasing the lysozyme content of the tears, but it had not proved of any particular value.

In reply to Dr. Barker's question, he stated that onions caused no increase in lacrimation in these patients, but only added to the discomfort of others in the room.

In discussing Sjögren's paper with Dr. Blackman, the description of eosinophiles in the lesions suggested to him the possibility of hypersensitivity and, as another cause, the dilated ducts suggested that they might be obstructed. Only one of the patients had been tested for hypersensitivity and the study had yielded negative results.

*3. The Diagnosis and Treatment of Ruptured Intervertebral Disc.* DR. W. E. DANDY.

SUMMARY

In opening the discussion Dr. Dandy recalled his first case of intervertebral disc, a patient referred to him by Dr. Llewellys Barker, thought to have malignant disease. His experience with discs now exceeds 1000 cases.

The diagnosis can be made on clinical grounds—by the history of *recurrent attacks* of low backache with sciatica, both increased by coughing and sneezing. The diagnosis is 98–99% perfect. In the neurological examination, diminution or absence of the Achilles reflex is almost the only important objective evidence and this is present only when the 5th lumbar disc is involved. The knee jerk is affected if the lesion involves the 3rd lumbar disc. Pain radiating down the back of the leg points to a lesion at L IV or L V whereas pain down the front of the leg indicates a

lesion at L III. In 95% of the cases, the lesion occurs at L IV or V or both: the remainder are mostly at L III, L II being very rarely involved. In 80% of the cases more than one disc is affected and in many instances recurrences are due to the same condition in another disc. The x-ray is frequently of assistance, narrowing of the disc being demonstrable in 50% of the cases. Injections of the spine are not necessary to make the diagnosis and are to be condemned. Air in the spine is very painful. Lipiodol, which was formerly extensively used, reveals the site of the lesion in one third of the cases only, and air even less frequently. Lipiodol is not absorbed and may lead to an inflammatory reaction as was well illustrated in a case which Dr. Dandy described.

The differential diagnosis from neurasthenic backache should involve no great difficulty; the pain in neurasthenic backache is constant. Tumors of the cauda equina or of the lower vertebrae are, however, indistinguishable from disc before operation. Eight such cases have been encountered during a period in which more than 1000 discs have been seen.

The "concealed disc" is scarcely more difficult to recognize. It probably does not protrude enough to cause compression of the nerve root and cause sciatic pain. In all probability the pain in these cases comes not from the disc itself but from the articular facets of the vertebrae, due to increased mobility of the joints.

At operation the affected disc can readily be located by testing its mobility with a periosteal elevator, a procedure shown to Dr. Dandy by Dr. Lenhard in another condition. A loose vertebra invariably means a defective disc. All affected discs cause abnormal mobility in this test, the one exception being a disc which has been completely, or nearly completely, absorbed.

The operation as now carried out involves an *almost complete* removal of the affected disc. Only a bit of a lamina is removed in the exposure. Only since June 1943 has such a complete removal been practiced and the results have apparently been most satisfactory. After removal of the disc, the vertebral bodies fuse together. Some postoperative pain is frequently present. This, Dr. Dandy believes, comes from the articular facets, but ultimately disappears as fusion becomes complete. Recurrences of pain are due either to involvement of a new disc or from a failure to recognize that more than one disc was originally affected. The simplicity of the operation and its excellent results are to be contrasted with bone graft fusion operations involving a long convalescence in a cast.

### DISCUSSION

*Dr. Blalock* pointed out that Dr. Dandy had always encountered skeptics in his work; nevertheless he was a dangerous man to disagree with, for in the long run he usually proved to be right. The skeptics were not lacking in the case of the disc. When Dr. Dandy first described this condition in 1928, his words fell on deaf ears, a sharp contrast to the situation today when every medical man was disc-conscious and even the chiropractors were getting interested in it.

*Dr. Robert W. Johnson, Jr.* stated that he appeared in the role of a shorn lamb, for the neurosurgeons had shorn the orthopedic surgeons of many backaches and

"headaches." By tradition, the lion and the lamb could not lie down together and he felt he must disagree with Dr. Dandy in a number of particulars.

He felt that orthopedic surgeons were in a better position than neurosurgeons to obtain a long-term picture of backache. They had been treating such patients for years and saw the late results of many forms of treatment. Dr. Johnson's own experience encompassed at least six forms of therapy for low back pain: manipulation of the sacroiliac, stretching the hamstrings, injections of the sciatic nerve, muscle dissections, exercises and braces, fusion operations and, lately, the disc operations. The immediate results of these procedures were often highly satisfactory, but not infrequently the patients came back later with recurrences. One must recognize that a great many diverse pathological conditions could lead to low back pain, among which he could mention: congenital defects of the spine, spondylolisthesis—which often gave late symptoms, fractures of the vertebral bodies, the facets or laminae, arthritis of the hypertrophic or the infectious type, the so-called Marie-Strumpell type of arthritis, sacroiliac tuberculosis, tuberculosis of the lumbar spine involving the discs as well, herpes zoster (a very confusing condition in the pre-eruptive stage); an instance of a needle in the sciatic nerve caused one case which he was familiar with.

Dr. Johnson felt that Dr. Dandy was promoting a dangerous idea before an open gathering by saying that an accurate diagnosis could be made on the basis of the history and an examination of the Achilles reflex. A case to be operated on should first be given the benefit of the most thorough clinical study by differential diagnostic methods. He agreed with Dr. Dandy, however, that lipiodol involved a greater risk than was justified by the knowledge gained.

Dr. Johnson paid a tribute to Dr. Dandy for the recognition and remedy of a lesion which undoubtedly causes sciatic pain. The lesion is a beautifully demonstrated and clear-cut one; moreover, it is a common one. Nevertheless, the need for being critical in diagnosis must be stressed, and he felt that the last word had not yet been said in regard to therapy. The operative procedure, particularly with the recent improvements—the complete curettage with a minimum of exposure—is probably better done here than anywhere else. He also pointed out that experience with fusion operations demonstrated the difficulty of getting bony fusion even with use of additional grafts, and he doubted whether solidification could be obtained by necessarily incomplete curettage of the fibro-cartilage of the disc—he had never seen such a solid fusion demonstrated by x-rays after any disc operation. Finally, he pointed out that many operations produce stresses and strains that become evident only with time. It is impossible to say how much difficulty these subjects may experience later from the articular facets. A follow-up of at least 5 years is required before the results can be fairly evaluated.

*Dr. R. E. Lenhard* praised Dr. Dandy's excellent contribution to a troublesome clinical picture, but shared Dr. Johnson's reservations. The diagnosis was not as simple a matter as Dr. Dandy maintained and every attempt should be made by clinical tests to exclude the other causes of low back pain that Dr. Johnson had mentioned, notably the different forms of arthritis. He agreed that lipiodol was

inadvisable and felt that the diagnosis should be made by clinical tests. Not infrequently, however, these were inconclusive. He stressed the importance of pain on coughing and sneezing as a manifestation of a disc in a back with reasonably good motion.

The therapy had been presented clearly by Dr. Dandy and undoubtedly was well handled by him, but he believed that it might not be indicated in all cases. There was no doubt that some would get well without operation. Possibly the fragmented part would be absorbed or would be fixed by the formation of scar tissue. We did not know how frequently this would occur.

## BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

*The Compleat Pediatrician.* By WILBURT C. DAVISON. 4th Ed. 256 pp. $3.75 Duke University Press, Durham, 1943.

This is the fourth edition of Dr. Davison's book. The preface emphasizes the fact that the volume is "an effort to compile and record briefly those practical pediatric facts, which though essential, usually slip from memory." The Compleat Pediatrician does contain an amazing amount of useful information, clearly stated and readily available. There are sections which list the diseases involving the various systems of the body, briefly enumerating the important signs and symptoms of each. However, the sections on laboratory procedures, general treatment and nursing, drugs and prescriptions appear to be of most practical value and cover material which is usually lacking in standard pediatric text books. Such techniques as cisternal puncture, parenteral administration of fluids, skin testing, etc., are rather fully described and make the book most useful to the interne in pediatrics or to the practitioner who is required to carry out these procedures. In the section on laboratory methods are listed tests in common use in the study of diseases of children, given in sufficient detail to warrant its use as a laboratory manual. The practicality of this little book may be illustrated by the fact that it even includes a section listing essential drugs and equipment for a pediatrician's bag. The title page of the Compleat Pediatrician states that it is written for the use of medical students, internes, general practitioners and pediatricians. The book appears to be of little value as far as medical students are concerned. It is far too practical for their purposes and by its very nature cannot elaborate on the fundamentals necessary for basic training in pediatrics. As a reference book, the Compleat Pediatrician does have its place in the library of the interne, general practitioner and pediatrician.

S. G.

*A Workbook of Elementary Pharmacology and Therapeutics* (Second Edition). By LUELLA C. SMITH. 300 pp. $2.00. The C. V. Mosby Company, St. Louis, 1943.

This book is intended to be a study guide in materia medica and therapeutics for student nurses. About one-half of the manual is devoted to problems in simple arithmetic, preparation of solutions, and dosage formulation; these exercises should give the student adequate training in calculations involved in administration of drugs. One chapter deals with the management of the ward medicine cabinet and the dispensing of drugs to patients. Special sections describe the administration of insulin and sulfonamide drugs. A chapter of elementary laboratory exercises is also included. Five chapters describe briefly the common astringents, antisep-

tics, and disinfectants; unfortunately, clarity has been sacrificed to brevity in this section, and some of the statements may mislead the student. An outline of introductory materia medica is also provided.

The workbook is bound in a loose-leaf binder, permitting use of the numerous pages of problems as class exercises.

A. C. B.

*Reconstructive Surgery of the Eyelids.* By WENDELL HUGHES. 160 pp. Illus. $4.00. The C. V. Mosby and Co., St. Louis, 1943.

This short volume is divided into ten chapters. The first four chapters are little more than an historical review of the development of plastic surgery from early Roman times to the present day. Few details are given, and, unfortunately, the illustrations employed to depict the various advances in plastic surgery are not altogether clear. This portion of the volume is, therefore, little more than a list of names and events, and contains little actual information for the reader.

The latter part of the book is distinctly better. The reconstruction of the conjunctiva, tarsus, lids, and lid borders are specifically discussed, but sometimes all too briefly. Rather than describe the detail of technical procedures, reference is made to the original articles. Case reports are used to illustrate various plastic operations, and these reflect the author's well known skill as an ophthalmic plastic surgeon. The figures and photographs are good, but the legends at times are inadequate.

In the main, this book will be of greatest value to the plastic surgeon confronted with problems involving the lids and ocular adnexa. The ophthalmologist, none too familiar with the various specialized techniques employed by the plastic surgeon, will probably find the descriptions too concise and abbreviated for his needs.

N. L. S.

*Reaction to Injury. Pathology for Students of Disease.* By WILEY D. FORBUS. 797 pp. Illus. $9.00. Williams & Wilkins Company, Baltimore, 1943.

It is a natural human tendency to attempt to classify, and thus to simplify the understanding of observed phenomena. In fact, this is the method of science. But it is necessary to check this tendency by logical criteria to prevent over-simplification and resultant confusion. This book represents an attempt to simplify the study of pathology by classifying all diseases into three groups, "*resistive*", "*submissive*" and "*adaptive*".

To force all disease entities into one of these three groups is over-simplification indeed, for it ignores the fact that in almost every disease reactions occur which could be interpreted as exemplifying all three of these terms. Furthermore, the classification is not objective, but rather approaches the teleological.

The work is divided into four parts. Part One presents the argument in support of the above classification, as well as chapters on etiologic factors. Part Two consists of an analysis of the "resistive", or inflammatory, reaction followed by discussions of the diseases which are thought to exemplify it. Parts Three and Four,

dealing respectively with the "submissive" and "adaptive" reactions are still in preparation.

The reviewer finds it difficult to understand the criteria which have been applied in the selection of the diseases discussed in Part Two. The author states that "A disease entity must be grouped . . . according to its dominant or primary reaction." How, then, can be justified the inclusion of such diseases as "degenerative arthritis deformans", nephritis and rheumatic fever among those characterized as "resistive"? The very essence of rheumatic fever is the destruction of collagen. This is hardly a "resistive" reaction. Furthermore, the "adaptive" phenomena which occur in the heart are far more "dominant" reactions in this disease than is the inflammation.

The discussions of the diseases are good. The chapters on the causes of disease, such as heat and radiant energy, are excellent. In them the tissue changes resulting from the various injurious agents are more completely described than in any other currently available text.

The book is profusely and, for the most part, excellently illustrated. The Kodachrome reproductions are poor.

The reviewer must take strong exception to the author's statement that this volume is a suitable text for the second year student in pathology. In addition to the objections already made, the scope of this work is too limited, dealing as it does with only one of seven or eight major fields that must be covered in the usual survey course.

J. E. G.

*A Hundred Years of Medicine.* By C. D. HAAGENSEN and WYNDHAM E. B. LLOYD. 444 pp. Illustrated. $3.75. Sheridan House, New York, 1943.

The present book is a considerably enlarged American edition of Wyndham E. B. Lloyd's book published under the same title in England in 1936 in *Duckworth's 100 years series*. Since Lloyd's interest is primarily in public health, his book was largely devoted to the history of that subject and gave a brilliant account of the rise of public health and social medicine chiefly in England during the last hundred years, pictured against the background of health and medical conditions at the beginning of the last century. The author did not attempt to cover the history of internal medicine, surgery or the specialties, and within these admitted limitations the book was and still is an excellent one.

The new edition was prepared by an American surgeon, C. D. Haagensen. He preserved a number of chapters of the old edition and retouched them by bringing in the American scene. But then he added a great number of new chapters discussing very competently advances in internal medicine and particularly in surgery, his own field. The result is a new book and a very good one that will be equally appreciated by medical students, physicians and laymen. The book is lavishly illustrated with pictures that are not generally known and the bibliography is considerably enlarged.

Personally, I think that it would have been better if Haagensen had not touched

Lloyd's book but had written a totally new one, because both books are conceived along different lines and the new edition does by no means replace Lloyd's original version. If a third writer should come and prepare a third version he would probably have to add a great deal also, notably a whole section on psychiatry, a field that is not touched at all but obviously belongs into a survey of the last hundred years. The subject is so broad that it is impossible to exhaust it in a one-volume book addressed to a general audience. All that can be done is to have it approached from various angles. Iago Galdston's *Progress in Medicine* (New York, 1940) was a very good such attempt, that did full justice to psychiatric developments. Lloyd's was another one from the public health angle, and Haagensen has a great deal to contribute in the field of surgery. All such books put together give an adequate picture of the last hundred years, but it is impossible to combine them into one book because the result will never be a harmonious whole.

H. E. S.